August 26, 2003

Dockets Management Branch, HFA-305
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket 95N-0309
Current Good Manufacturing Practice, Quality Control Procedures, Quality Factors, Notification Requirements and Records and Reports, for the Production of Infant Formula

Dear Sir or Madam:

This letter is prompted by the April 28, 2003 reopening by the Food and Drug Administration (FDA or "Agency") of the comment period for the proposed rule published by the Agency entitled, "Current Good Manufacturing Practice, Quality Control Procedures, Quality Factors, Notification Requirements, and Record and Reports, for the Production of Infant Formula" (61 *Federal Register* 36153; July 9, 1996). These comments are submitted on behalf of all the major U.S. infant formula manufacturers by the International Formula Council ("IFC"), the association representing manufacturers of infant formula in the United States.[1] These comments address the new issues raised by the agency when reopening the comment period and reflect the IFC current position on each provision of the proposed rule. These comments replace the December 6, 1996 comments submitted by IFC in response to the original proposed rule.

Format of IFC's Comment to the Proposed Regulation

These comments contain two major sections: General Comments and Specific Comments. The **General Comments** include comments that apply to the proposed

[1] International Formula Council members are: Abbott Laboratories, Ross Products Division; Bristol-Meyers Squibb Company, Mead Johnson Nutritionals; Nestlé USA, Inc., Nutrition Division; Solus Products; and Wyeth Nutrition.

regulations as a whole and to requests for comments by the Agency to multiple sections. **Specific Comments** address individual sections of the proposal. When, in a Specific Comment to a proposed section, a General Comment applies, it will simply be referenced and not repeated. In April of 2003, seven additional issues within the scope of this proposal, which had come to the Agency's attention since the 1996 proposal was published, were set forth in the announcement of the reopening of comments. Rather than address all of them separately at the outset, we have chosen a few key issues to address in the General Comments, and have woven the rest of our comments on those issues into the Specific Comments wherever they are the most relevant.

Each of the IFC's Specific Comments will be preceded by two columns. The language proposed by FDA will be in the left hand column, and the language that the IFC would suggest be substituted (or other action, if any), will be described in the right hand column. In those instances when changes are suggested, a "redlined" version will also be provided immediately beneath the FDA-proposed and IFC-suggested language to assist in the understanding of the desired change(s). When utilized, this will show by strike-through words that IFC suggests deleting and by shading the words that IFC suggests adding.

The entire text of the IFC's suggested language is included in these comments (Attachment A), as is a redlined comparison of the IFC's suggested language with language proposed by FDA. (Attachment B)

IFC's General Comments to FDA's Proposal

I. IFC's Appreciation of FDA's Effort and the Importance of GMPs

The 1996 proposal was the result of a significant effort by FDA. When Congress enacted legislation that required FDA to promulgate Good Manufacturing Practice ("GMP") Regulations specific to infant formula, the Agency worked hard to familiarize itself with the manufacturing methods of these important food products. As mentioned by FDA in the preamble to the 1996 Proposed GMP Regulation, several people at FDA responsible for the preparation and drafting of the proposal have visited the manufacturing facilities of the IFC members for the purpose of learning something about each manufacturer's unique manufacturing systems and processes. The results of these efforts were evident from the proposal. Generally, the 1996 proposed regulation was a good initial effort at establishing a GMP regulation for infant formula that was flexible enough both to accommodate each manufacturer's current manufacturing methods, and to allow for incorporation of the inevitable improvements in technology that the future holds. There were, however, a number of very significant concerns with the proposal that the IFC addressed in its comments to the 1996 proposal. As discussed below, had FDA reviewed the IFC's and other comments to that initial proposal, and reproposed a GMP regulation for infant formula incorporating the Agency's conclusions based on those comments, the process would be significantly more advanced than where it is now.

We would like to underscore that IFC's comments are not lightly made, given the importance all industry members attach to GMPs. In the absence to date of a thorough

system of specific regulatory requirements relating to GMP, the industry has developed a comprehensive course of good manufacturing practice and developed a commensurate level of internal expertise on manufacturing issues, all of which is well illustrated by the industry's excellent record of manufacturing safe, high-quality infant formula products over the more than 20 years since the passage of the Infant Formula Act. In light of the importance that the industry attaches to the manufacturing of the important product it produces, the FDA must recognize that the industry's expertise on issues affecting infant formula manufacturing is at least equal to if not greater than the expertise that is resident within FDA. As we proceed with our comments, it may be noted that a careful review of the authorities cited in support of the 1996 proposed requirements calls into question the existence of concrete bases for a number of the proposed "requirements" and, thus, appears to reflect "administrative" expertise and thinking as opposed to the practical hands-on experience the industry possesses. We trust that our practical expertise will be accorded the credence that it is due during the Agency's attempt to resolve any remaining issues.

II. Specific Objection to April 28, 2003 Notice

Before getting to the substance of our comments, IFC would like to express the surprise experienced by the infant formula industry at the nature and timing of the Agency's re-proposal. For years we have been told by Agency personnel, albeit informally, that the GMP regulations were in the process of being finalized. Now, instead of offering a meaningful FDA response to our past comments on the 1996 proposal or on the major initiatives brought before the FAC, the Agency, without any indication of where it may be headed, has merely asked for our commentary again. We respectfully object to the process FDA has followed as one that shields from industry comment the thinking and direction FDA has on the critical issues at the heart of this initiative.

The Agency's April 28, 2003 "reproposal" of the GMP rule is particularly frustrating because it raises new issues not previously covered by the original proposed rule and fails to provide any guidance on how the Agency proposes to address these new issues. For example, the reproposal requests extensive information on whether there is a need to include a microbiological requirement in the final regulation for *E. sakazakii* and whether the microbiological requirements for powdered infant formulas intended for premature and newborn infants should be higher than those for older infants. The reproposal raises these and other issues that are beyond the scope of the original proposal and fails to offer proposed regulatory language that would provide insight on how the Agency intends to address these new issues in a final regulation.

The Agency's initiative seems at odds with the fundamental obligation of an agency under the Administrative Procedure Act ("APA") to make its views known to the public in a concrete and focused forum so as to make criticism or formulation of alternatives possible. *See Home Box Office Inc. v. FCC*, 567 F.2d 9, 36 (D.C. Cir. 1977), *cert denied* 434 U.S. 829 (1977), and *rehearing denied*, 434 U.S. 988 (1977). The APA requires that a notice of proposed rulemaking must include "either the terms or substance of the proposed rule or a description of the subject or issues involved." The notice's general format places the subjects and issues into a historical but not analytical context. In the process, the notice fails to

describe the range of alternatives actually being considered by the Agency and gives no indication where FDA is headed either on a response to the extensive comments it received on the 1996 rule, or on how it is leaning toward resolving those issues. As a result, we are forced to comment on rules we may not see until they are purportedly "final".

A key hallmark of the administrative notice and comment rulemaking process is providing fairness to interested parties. *See Small Refiner Lead Phase-Down Task Force v. EPA*, 705 F.2d 506, 547 (D.C. Cir. 1983). Fairness includes the opportunity to comment meaningfully on the substantive regulations that will apply. A key prerequisite for meaningful comment is the Agency's rationale connecting data and law to the regulation being proposed. *See Florida Power and Light Company v. United States*, 846 F.2d 765, 771 (D.C. Cir. 1988). As contemplated under the APA, the rulemaking process is meant to be a shared enterprise that empowers the public to question the proposed regulation and the data and assumptions on which it is based before it becomes effective. In issuing the "reproposal" of the GMP final rule, the Agency has failed to meet the foregoing goals of rulemaking. Thus, the IFC strongly believes that an additional round of notice and comments must follow this "reproposal" especially to the extent that the Agency intends to draft regulations addressing the new substantive issues not found in the original proposed rule.

III. FDA's Request for Comments - Key Issues

FDA and IFC share the mutual goal of assuring that a final GMP regulation emerges from the notice and comment process that achieves a number of important public health objectives, including:

- Fostering innovation and quality in infant formulas; and
- Establishing only provisions that avoid unnecessary costs and add value to the product, i.e., only provisions that increase assurance that infant formulas are safe, wholesome and fulfill their important function in infant nutrition.

To those ends, we have addressed several of FDA's seven questions throughout our comments and would like separately to address three key issues raised in the FDA's April 28 notice reopening the comment period. Two of these issues – the emergence of *Enterobacter sakazakii* (*E. sakazakii*) and the assessment of normal growth – also have been addressed recently by FDA Food Advisory Committees.

FIRST ISSUE: *ENTEROBACTER SAKAZAKII* (FDA's Issue 1)

In light of the discussions held at the March 18-19, 2003 meeting of FDA's Food Advisory Committee, Subcommittee on Contaminants and Natural Toxicants (CNTS), IFC would like to emphasize that there is no need to establish a specific microbiological requirement for *E. sakazakii*. Infrequent but disturbing reports have been published during the course of the last 20 years indicating that *E. sakazakii* is an opportunistic microorganism capable of causing serious infections in low birth weight and immunocompromised infants. (*E. sakazakii* is an opportunist in that it may only be a significant threat to health in these

abovementioned, specific highly susceptible populations.) Suggestive evidence does establish a possible association with powdered infant formula. However, where there has been an association with powdered infant formula, infections are almost exclusively associated with preparation and use of reconstituted powdered infant formula in hospitals. Thus, reported infections may be related to the vulnerability of the hospital population and deviations from infant formula good hygienic handling practices, as developed by the American Dietetic Association. Premature infant infections associated with *E. sakazakii* are rare; and term infant infections associated with *E. sakazakii* are rarer still. This is consistent with a recent publication from Health Canada using a suckling mouse model that found this organism has low infectivity, and that large numbers of organisms are needed to cause infection, even with the most virulent strains. The available evidence provides the Agency no basis for regulatory concern even when measured by the Act's conservative safety standards.

Although the available scientific evidence does not permit a comprehensive risk assessment, the available evidence does permit the rather straightforward conclusion, like that reached by the Food Advisory Committee, that whatever risk to term infants that powdered infant formula may pose by virtue of the presence of *E. sakazakii*, that risk is not only lower than that which is associated with premature infants but also is unquantifiable. Although the issue merits further exploration like the Codex Alimentarius Commission's risk assessment initiative, there is no basis upon which FDA can support any conclusion that suggests that *E. sakazakii* presents an actionable risk of harm to healthy term infants. For these reasons, IFC does not believe it is necessary to establish a specific microbiological requirement for *E. sakazakii* in infant formulas.

The April 28 Notice asked in particular whether powdered infant formula to be consumed by premature and newborn infants should meet stricter microbiological requirements than formula intended for older infants.

There is scientific and medical rationale, supported by both experience and provisions in the Infant Formula Act, to set different standards for formulas intended for premature (low birth weight) infants than those for term infants. There is no apparent basis to set different standards for healthy term newborn infants and older infants born at term, except in the sense that older term infants who are weaned are subject to the microbiological standards applicable to the general food supply.

The example of different standards for premature and term infants is made by inspection of published information on infection by *E. sakazakii*. The literature on *E. sakazakii*-associated illness cited by FDA in its presentation to the March 18-19, 2003 CNTS of the FAC was examined to assess what evidence may implicate formula as a possible cause of *E. sakazakii*-related disease among healthy term infants.

In summary from the data reviewed,[2] the total reported cases of *E. sakazakii* infection

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[2] There are four reports of *E. sakazakii* disease among healthy term infants. Monroe and Tift (1979)

in infants born at term and greater than 2500 grams is four infants. In two cases (Block et al., Monroe and Tift) there is only an association of *E. sakazakii* infection with formula feeding. In one other case (Muytjens et al.), there was positive evidence of contamination from hospital equipment where tests of powdered formula itself were negative, and in the fourth report (Biering et al.) the authors note mishandling of reconstituted formula by "extended periods of time in bottle heaters." Handling practice is clearly important; the data from CDC and others presented at the FAC meeting showed that there was virtually no growth of *E. sakazakii* at 4 degrees C and that the doubling time at room temperature is about 40 minutes.

The absence of reported cases does not mean that there have been no occurrences among healthy term infants. But it does suggest that the presence of extremely low levels of the organism as reported by the FDA, Muytjens et al. 1988, and the recent Canadian survey, is not sufficient by itself to pose a risk. The only reported occurrences of disease in healthy term infants where the reconstituted formula was shown to be contaminated also had evidence of external contamination or mishandling of reconstituted product. Given the low risk of *E. sakazakii*-associated illness in healthy term infants from properly prepared formula, FDA's current *de facto* standard of zero tolerance of *E. sakazakii* in formulas for term infants is not warranted.

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reported bacteremia in one male term infant (birth weight 2600 g) that had been fed formula, but did not provide evidence that the formula was causally related to the infection. They write, "The epidemiological aspects concerning the reservoir and route of transmission of the organism in relationship to this case are uncertain."

Muytjens et al. (1983) reported on 8 infants, one of who was described as full term and had a birth weight over 2500 g. *E. sakazakii* was isolated several times from prepared formula, a stirring spoon and a dish brush; but was not isolated from formula powder.

Biering et al. (1989) reported 3 cases, 2 of which were more than 38 weeks and above 2500 g, but one had gastrointestinal surgery. The other was fed on breast milk and powdered formula. These investigators attempted to isolate the organism from the environment, including powdered formula. They could not isolate the organism from "numerous" cultures of freshly prepared formula, but could if reconstituted powder was incubated for 4 hours at 36 degrees C. They suggest that the reason some infants got sick and others fed the same formula did not: "The most likely explanation appears to be that the rules pertaining to the handling of the formula in the wards were not always adhered to. There is some anecdotal evidence that the formula bottles were occasionally kept at 35 to 37 C for extended periods of time in bottle heaters, thus allowing for multiplication of the organism." This is the strongest evidence to date that there may be a risk of disease if formula is mishandled. However, there are many forms of mishandling of formula that could constitute a risk to the health of infants.

Finally, Block et al. (2002) conducted a look-back through hospital records from 1987 onward for cases of *E. sakazakii* infection. Their database, from two hospitals each delivering 3000-3500 infants annually, found one case of bacteremia in a term infant that had been formula fed, but the formula itself was not analyzed and there is no further information about the case.

Further rationale that supports a separate standard for low birth weight (LBW) and at-risk infants is found in section 412(a)(1)(A) and (B) of the FFDCA, which exempts formulas represented and labeled for use by infants who are LBW or who have unusual medical problems (such as would require hospitalization) from the good manufacturing practices established under 412(b)(2)(A), that include microbiological specifications.

The CNTS of the FAC met on March 18-19, 2003, and was in agreement that there is a very small risk, though not quantifiable because of the absence of data, that healthy term infants could develop illness because of *E. sakazakii* contaminated formula. According to the minutes, "The population at risk are preterm infants born at less than 36 weeks gestational age up to a post term age of 4-6 weeks, immunocompromised infants at any age, and term infants hospitalized in level 2 and level 3 neonatal intensive care units." Healthy term infants are not included among those identified as "at risk" but were separated by FAC from at-risk groups.

The FAC determined "There is probably a low but as yet unquantified risk in healthy term infants, which cannot be described with data available at this time." What does "probably a low but as yet unquantified risk" mean? Most simply, it is the qualified language of an academic group that knows to be careful to avoid absolutes. There is "probably a low but as yet unquantified risk" of all kinds of maladies. The risk is so remote that healthcare or behavioral decisions are not made on the basis of that risk.

FDA should be reluctant to extrapolate an estimate of risk that is developed primarily from data and information involving preterm infants to a risk among healthy term infants. The FAC that met April 4-5, 2002 discouraged this type of extrapolation for other safety assessments, such as growth (although FAC did express frustration that safety and growth were used interchangeably by FDA). At the April 4-5, 2002 meeting of the FAC, preterm infants were described as very different than term infants with respect to medical needs, nutritional needs and vulnerability to disease. While older preterm infants (e.g., 32-36 weeks) have digestive and absorptive capabilities sufficient to absorb the nutrient levels found in preterm formula many young preterm infants have not yet developed a mature intestinal barrier function. Other preterm infants may have dysmotility or compromised GI function that could result in greater vulnerability to potential pathogenic bacteria in the intestine. Consequently, in the assessment of risk of disease from GI pathogens, there is need to consider separately infants according to post-conceptional age.

IFC believes that *E. sakazakii* can be more effectively controlled through routine surveillance of indicator organisms, coupled with strong Hazard Analysis Critical Control Point (HACCP) programs, labeling and education. Although proactive measures may be taken to reduce the level, frequency, and incidence of *E. sakazakii* in powdered infant formula, total eradication of the microorganism from powdered infant formula is not currently technologically possible given the nature of food powder manufacturing. U.S. Infant Formula Manufacturers, in cooperation with government and the healthcare community, have embarked on an aggressive and ambitious program to further define and reduce, to the extent possible, any potential risk posed from powdered infant formula. The immediate focus and responsibility of the industry has been to identify and implement

labeling and education, and manufacturing measures and to lay the groundwork for a series of steps to reduce the potential for the microorganism to reach levels (in the powdered can, in the bottle, or in the feeding tube) that would constitute a hazard to health.

IFC contributed several documents for the consideration of the FAC Subcommittee on Contaminants and Natural Toxicants meeting to discuss *E. sakazakii* in March 2003 and thereafter. The dialogue on this topic between IFC and FDA is ongoing, and we believe it is premature to comment further in this context. Since the Agency has specifically requested comments on this topic for the docket on the proposed GMPs, we have attached those documents we previously contributed as an appendix to our comments. Those documents include:

- IFC's June 20, 2003 letter to Dr. Christine Taylor re Industry Proposal on Infant Formula Powder Labeling (Attachment C)
- IFC's June 27, 2003 letter to Dr. Christine Taylor re Proposed Discussion Points on Powdered Infant Formula Good Manufacturing Practices (Attachment D)
- IFC's July 7, 2003 letter to Dr. Christine Taylor re Special Products (Attachment E)
- Douglas L. Archer's July 7, 2003 letter to Robert C. Gelardi re Summary of Industry Data re Testing for *E. sakazakii* in Powdered Infant Formula – Submitted to Dr. Christine Taylor on July, 7, 2003 (Attachment F)

SECOND ISSUE: ASSESSMENT OF NORMAL GROWTH (FDA's Issue 6)

In light of the discussions held at the two 2002 meetings of the FDA's ad hoc Infant Formula Subcommittee of the Food Advisory Committee, IFC has taken a new look at the basis for this proposed "quality factor". As explained below, IFC believes that the Agency's effort to establish "normal growth" as a required quality factor is flawed and should be abandoned. The clearest definition of "quality factor" comes in one line from the legislative history: "Quality factors pertain to the bioavailability of a nutrient and the maintenance of level or potency of nutrients through an expected shelf life of the product."[3] FDA may have based its concept of "healthy growth" on another line in the legislative history to the effect that "the growth of infants during the first few months of life often determines the pattern of development and quality of health in adult life." This statement was apparently used to emphasize the conclusion that appears at the end of the same paragraph: "the availability of infant formula which is safe and nutritious is critically important to the health of our nation."[4]

As responsible manufacturers of infant formula, the industry absolutely agrees with the critical importance assigned to ensuring the bioavailability of infant formula, and agrees with Congress' obvious concerns about bioavailability and nutrient potency throughout shelf life. Growth is clearly an indicator of bioavailability and, as such, can be an important point to consider when a question of bioavailability is raised. But, few changes in an infant

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[3] *See* House Committee on Interstate and Foreign Commerce Report: The Infant Formula Act, p. 6.

[4] *Id.* at p. 5.

formula raise such questions, and the routine demonstration of growth relative to most changes in an infant formula cannot be considered a specific legal "requirement." Thus, we object on legal, scientific, and policy reasons to the proposed establishment of evidence of "normal growth" (or "healthy growth" according to the April notice) as a quality factor to be looked for on any regular basis.

Legal Issues: The Infant Formula Act states that the Secretary "shall by regulation establish requirements for quality factors for infant formulas to the extent possible consistent with current scientific knowledge, including quality factor requirements for the nutrients required by subsection (i). Federal Food, Drug, and Cosmetic Act (FFDCA) § 412(b)(1). The Infant Formula Act makes no mention of "normal growth," nor does it define "quality factors." The FFDCA makes it clear that quality factors could be established for components in the formula such as protein quality and the quality of other nutrients that may be added to the infant formula. By defining "normal growth" as a quality factor, the Agency essentially would be establishing a requirement that applies to the entire infant formula matrix and not merely a component found in the infant formula. There simply is no basis in the plain language of the statute or the legislative history to support such an interpretation of quality factor.

Indeed, a review of the legislative history establishes that both Congress and FDA in comments to the bills under consideration, considered quality factors to be limited to individual components in the infant formula. In the Senate record pertaining to the 1986 amendments Senator Metzenbaum described the 1986 amendments as providing testing for "each essential nutrient" and further described "the quality factor of nutrient content requirements of the law, as demonstrated by the testing called for in the amendments." In its comments on the 1986 amendments, FDA informed the Senate that the state of knowledge and science with respect to quality factors was still evolving, and that, therefore, there was a basis for only one quality factor for a nutrient [referring to protein efficiency ratio]. 132 CONG. REC. S14042, 14046 (daily ed. Sept. 27, 1986) (statement of Sen. Metzenbaum)). These statements evidence a Congressional intent, and an agency agreement with such intent, that quality factors would be established for components in the formula. Moreover, the Agency remarks indicate that at the time of passage of the Infant Formula Act Amendments, FDA envisioned the establishment of only one quality factor, namely for protein efficiency ratio. FDA could have identified growth as a quality factor then but did not, so that such an interpretation was not before the Congress when it considered and enacted the 1986 amendments. Moreover, in the legislative history of the 1980 Act, statements by Senator Metzenbaum and Mr. Gore refer to testing in the context of laboratory analysis of required nutrients, never in the context of clinical studies.

The establishment of "normal growth" as a quality factor essentially results in the imposition of mandatory clinical study requirements for infant formulas, unless the manufacturer would qualify for one of the narrow exemptions found in the FDA proposal. Under the Infant Formula Act, a premarket notification must be submitted before a manufacturer introduces into commerce a "new infant formula." The premarket notification must contain numerous data and information, including data demonstrating that the new infant formula meets the quality factor requirements established by FDA. "New

infant formula" is defined broadly to include (1) infant formulas manufactured by a person which has not previously manufactured an infant formula and (2) an infant formula manufactured by a person which has previously manufactured infant formula and in which there is a major change, in processing or formulation, from a current or any previous formulation produced by such manufacturer. FFDCA § 412(c)(2). The proposed rule contains a broad definition of major change that would mandate the filing of a premarket notification for numerous changes in processing and/or formulation. While the industry recognizes that clinical studies may be needed to assess some of these major changes (such as the use of a certain new ingredients with no prior history of use in infant formulas), there is no scientific basis to mandate clinical studies for other major changes (such as the manufacture of an infant formula on a new processing line).

The Infant Formula Act does not provide FDA with the legal authority to require infant formula manufacturers to conduct clinical studies for new infant formulas. The statute does not impose a clinical testing requirement and indeed, Congress specifically rejected an earlier version of a bill that would have imposed clinical testing. In testimony before the House of Representatives, then-Commissioner of Food and Drugs, Jere Goyan, interpreted the proposed legislation as requiring manufacturers of infant formula "to conduct tests, including clinical tests, where appropriate, to determine the safety of the formula and complete reports on the tests." *Nutritional Quality of Infant Formula: Hearings on H.R. 6590, H.R. 6608, H.R. 5836, and H.R. 5839 Before the Subcomm. on Health and the Environment of the House Comm. on Interstate and Foreign Commerce*, 96th Cong. 74 (1980) (Statement of Jere E. Goyan, Commissioner, Food and Drug Administration). In response to Dr. Goyan's testimony regarding clinical testing, Representative Mottl, co-sponsor of the bill stated: "[i]t is important that we define what we mean when we speak of testing. When I say testing, I am speaking of analysis in the chemical and nutritional laboratories, and I am not referring to clinical trials." *Id.* at 120 (Statement of Rep. Mottl, Member, House Comm. on Interstate and Foreign Commerce).

In addition, the 1996 proposal to define the general quality factor as a growth study is inconsistent with the "Guidelines Concerning Notification and Testing of Infant Formulas" incorporated into section 412(c)(2) of the 1986 Amendments to the Infant Formula Act (hereinafter "1986 Guidelines"; Attachment G). This section of the Infant Formula Act provides that "for purposes of this paragraph, the term 'major change' has the meaning given to such term in section 106.30(c)(2) of title 21, Code of Federal Regulations (as in effect on August 1, 1986), *and guidelines issued thereunder.*" FFDCA § 412(c)(2) (*emphasis added).* The phrase "*guidelines issued thereunder*" is a direct reference to the 1986 Guidelines. These Guidelines state:

> "FDA has recognized that premarket clinical evaluation in humans may be appropriate whenever certain changes affecting the nutritional profile of an infant formula are made, particularly in the case of new or reformulated products. FDA has also recognized that the degree and complexity of the clinical testing needed, will vary according to the extent of the changes in the formula. Until guidelines are developed, it is therefore understood that the scope of the clinical testing necessary for new and reformulated infant formulas will be decided by the manufacturer on a

case-by-case basis and that the chemical testing alone for major reformulation may not be sufficient to determine adequacy of the product."

Thus, the key points about clinical testing in the Guidelines were that:

- FDA anticipated *guidelines* for clinical testing, not mandatory requirements (indeed, as FDA had contracted a review by the American Academy of Pediatrics, subsequently published in 1988, it is likely that the Agency was anticipating AAP's Guidelines);
- There is acknowledgement that the *degree and complexity* of clinical testing would vary,
- The scope of the testing was to be *decided by the manufacturer*, and
- Testing was to be decided by the manufacturer on a *case-by-case basis*.

Importantly, in these Guidelines FDA acknowledges that there *may be* a need to go beyond chemical and nutritional analyses, as was described in the legislative history to the IFA, but does not suggest that the Agency would require a growth study for every change. Unfortunately, there is no discussion of this important document in the preamble to the 1996 proposed rule. Guidelines written under FDA contract by the American Academy of Pediatrics (1988) were careful to note that there were many situations in which a change in the composition of formula would not generate the need for clinical study, and other situations where the relevant clinical endpoints would not be growth, but biochemical indicators of nutritional status. That case-by-case consideration by AAP seems closer to the 1986 Guidelines than FDA's 1996 proposed rule.

In the 1996 proposal, FDA characterized the growth study recommendations made in the AAP's guidelines as quality factors. The identification of quality factors as a synonym for clinical studies seems to have developed after AAP's Guidelines, because the term "quality factors" never appears in the AAP document. Besides a routine growth study, FDA did not propose to make other types of clinical studies that were described by AAP (e.g., serum chemistries) into quality factors, and certainly did not define the need for growth studies in the focused way that AAP did. AAP was careful to limit the scope of testing of a formula to which a new component is added, noting, "a formula modification does not require testing of the formula components that are unchanged."

Scientific Issues: In addition to the absence of any legal basis, there are meaningful scientific weaknesses to establishing growth as a quality factor. FDA's proposal would require the manufacturer to conduct an adequate and well-controlled clinical study to determine whether an infant formula supports normal physical growth. This methodology is scientifically ideal to answer the question of whether a new substance added to an existing formula has an effect on the bioavailability of a nutrient required for infant growth. However, not every change in an infant formula raises questions as to infant growth that cannot be answered adequately by other scientific supportive data. [Russell J. Merritt's November 2002 Slide Presentation to FAC (Attachment H); Jon A. Vanderhoof's November 2002 Slide Presentation to FAC (Attachment I); Jose M. Saavedra's November 2002 Slide Presentation to FAC (Attachment J); IFC's "Decision Tree for Documentation of Nutritional

Adequacy of a New or Changed Infant Formula" submitted to the FAC in November 2002 (Attachment K); IFC's "Decision Tree Chart for Documentation of Nutritional Adequacy of a New or Changed Infant Formula" submitted to FAC in November 2002 (Attachment L).

FDA is correct to insist that new substances themselves that might be added to formula be GRAS. The GRAS notification process provides FDA a venue to raise any safety concerns, including concerns about matrix issues, processing issues or nutrient interactions. It is at this point that safety issues, including the potential for impact on growth, need to be raised and resolved. In order to prevent unnecessary and invasive clinical study, as much reliance as possible should be placed on animal studies. Routine growth studies are not designed and generally not powered to detect rarely occurring adverse events, so are not comprehensive safety studies. Nor should they be. The law fixes the composition of all essential nutrients in infant formula. New ingredients are often substances identified in human milk as having a nutritional function. A case-by-case review of available evidence can identify when there is a need for safety endpoints in clinical studies.

Policy Issues: As was obvious during the FAC discussions, not enough is known about what constitutes optimal growth to make it possible to choose the one perfect standard against which "normal" or "healthy" growth should be judged. Thus, as a matter of policy, it seems wasteful and wrong for a science-based Agency to place needless dependence on growth as an outcome. Focusing on a single outcome causes FDA problems in being even handed: how can the Agency allow one manufacturer to bring about an advancement and recover the cost of investment for a formula innovation, while not allowing all other manufacturers to use the same ingredient in their formulas. The only answer to FDA is to require each company to conduct a growth study on the same new substance, justified under the assertion that the "matrix" used by different manufacturers or some peculiar nutrient-nutrient interaction could result in one manufacturer's formula giving a lower growth response. This approach levels the playing field some, but begs the questions about the ethics of requiring redundant studies that do not improve public health and about the Agency's commitment to the protection of human subjects of scientific studies. Simply put, focusing on quality factors as what they are meant to be – indicators of bioavailability or potency – is far more sensible and far more consistent with the literal language of the statute, and helps avoid unnecessary and ethically unjustified testing.

Thus, the Agency should abandon the attempt to define a general quality factor as a growth study. Quality Factors should remain indicators of the potency or biological quality of a nutrient as originally defined. FDA should still have a provision for clinical studies but any requirement should stem from the language in the 1986 Guidelines. To this end, IFC proposes to add new regulatory provision in section 106.120 that would clarify the instances in which clinical studies would be included in a premarket notification for a new infant formula. The new section 106.120(b)(6) proposed by IFC is modeled after the language found in the 1986 Guidelines and would incorporate into the regulations the practices and procedures that have been in place for almost two decades. As will be discussed in more detail below in our comments to the new section 106.120(b)(6), a clinical study would be required to support a premarket notification for a responsible party that has not previously manufactured infant formula in the United States. The new provision also would clarify that

clinical studies may be necessary when a current manufacturer or responsible party predicts, based on experience or theory, that a major change could have a possible significant adverse impact on bioavailability of nutrients and when chemical testing or scientific information are unavailable to rule out such an adverse impact.

In the April 28 Notice, the Agency requested comment on what requirements the Agency should establish to determine when manufacturers must conduct clinical growth studies for a new or reformulated infant formula. (Issue 6a) The 1986 Guidelines provide the industry and the Agency the instruction to determine on a case-by-case basis when a clinical study is needed and what the nature of the study is. The new section proposed by IFC would address the instances when a manufacturer may conclude that a clinical study should be conducted to support a major change in formulation. This proposed provision recognizes that a clinical study is unnecessary when there are other available scientific information that can predict the impact that the major change will have on the bioavailability of the nutrients in the formula. [IFC's "Sample Clinical Growth Trial Protocol for Healthy Term Infants" submitted to the FAC in November 2002 (Attachment M)] This framework provides the flexibility that is needed to devote clinical research towards its most productive outcome.

Summary and Recommendations: For the legal, scientific and policy reasons explained above, IFC believes that FDA should not define "normal growth" as a quality factor. IFC also believes that FDA should delete the clinical study requirements contained in proposed 106.97(a). IFC recognizes that there are some instances in which it is appropriate to include clinical studies in a premarket notification and has proposed a new section 106.120(b)(6) to address this issue. IFC urges the Agency to adopt the new 106.120(b)(6) proposed by IFC because this provision mirrors the language found in the 1986 Guidelines, a guideline that has been sanctioned by Congress through its incorporation into the Infant Formula Act. IFC also believes that it would be appropriate for the Agency to include a statement in the preamble to the final regulation encouraging interested parties to meet with the Agency when exploring formulation and other changes to infant formulas for the purpose of deciding whether a clinical study would be needed and if so, to reach agreement on the type of study needed. Study design should remain the responsibility of the manufacturer, but should be mutually agreed to prior to study initiation.

The Agency also requested comments whether additional quality factors, specifically for fat, calcium, and phosphorus bioavailability, should be established. The IFC has provided its comments on this request in its specific comment to proposed 106.96(c).

THIRD ISSUE: CONTROL SYSTEMS AND STORAGE AREAS (FDA's Issue 3a)

A third key issue raised in the FDA's 2003 notice reopening the comment period – control systems for raw, in-process and finished materials – was extensively addressed in our 1996 comments and will again be addressed in these 2003 comments.

The proposal requires separate storage areas for raw materials, in-process goods and finished product goods to achieve physical differentiation for "pending release," "released"

and "quarantine." The IFC notes that this is impractical and unwarranted for the infant formula industry. While the IFC agrees that each manufacturer must establish an effective system to identify and to control product during all stages of production, physical separation is an extreme measure to require and is not justified. The raw materials for infant formula involve truckloads of bagged ingredients and packaging materials, as well as tank trucks or railcars of liquid ingredients. The sheer magnitude of the physical volume of materials, the monumental warehouse expansion needs and the significant headcount increases to accommodate the constant movement of materials to areas designated for the various control categories, would be enormous. In addition to the resource concerns with this proposal, the constant movement of such large quantities of materials would surely create quality problems, including increased risk of contamination and cross-contamination, spills, damage, etc. Infant formula manufacturers design, maintain and run their operations to be compliant with food current good manufacturing practices, 21 CFR 110.20(b)(1). This section of the regulations states:

> (b) *Plant construction and design.* Plant buildings and structures shall be suitable in size, construction, and design to facilitate maintenance and sanitary operations for food-manufacturing purposes. The plant and facilities shall:
>
> (1) Provide sufficient space for such placement of equipment and storage of materials as is necessary for the maintenance of sanitary operations and the production of safe food.

This current system is working, thus, there is no need to mandate physical barriers because such barriers are not always necessary. The manufacturer, when developing the design of the facility, is in the best position to determine the controls that need to be in place and the regulations need to maintain this flexibility.

Accordingly, the IFC proposes a quality-based alternative approach in its specific comments below.

Moreover, in current infant formula manufacturing practice, and throughout the food industry, systematic control of inventories (raw and finished) is common and widely used. These systems utilize controls in addition to or in lieu of strict physical segregation of un-approved and approved for use materials, in-process substances and finished products. The utilization of a computer based inventory status control, which requires that a worker seek out the status of a material prior to use, coupled with the required checks and verifications, should be sufficient in controlling the use of an ingredient or raw material. In the pharmaceutical industry, FDA has recognized this concept since the 1980s. What is important, and should be required, is that the status of any ingredient or raw material can be easily determined and controlled – whether by physical location, status tagging, records, or a combination thereof. Mandated physical segregation of materials based (solely) on status would be an unnecessary and unjustified burden upon the industry, as alternate means of material control have been and are being successfully employed in other GMP situations.

Comments specific to the other issues raised in the Agency's 2003 reopening announcement, including air filtration systems, calibration practices and microbiological controls, are included in the Specific Comments section.

IFC agrees with FDA's decision to remove clinical study protocol provisions from these proposed regulations (FDA's Issue 7). A number of comments pertaining to the contemplated Guidance document on clinical studies are included herein and more detailed comments will be provided separately at a later date.

IV. Impact Analysis and Effective Date of the Final Regulation

The impact analysis included with FDA's proposal concludes that infant formula manufacturers already comply with "many" of the requirements of the proposed rule. FDA's assessment of the status of manufacturers' compliance with the proposal as of 1996 is relevant not only to the financial impact of the final regulation, but also to the length of time that it will take for current manufacturers to achieve compliance with the final regulation. This premise forms the basis for FDA to adopt an "Option 2" analysis, which incorporates the assumption that the proposed regulation will be adopted as it was proposed (1996 Proposal at p. 36202).

Contrary to FDA's assessment, the IFC's analysis of the proposal has identified a number of significant proposed provisions with which manufacturers may not currently be complying with the specifics of the proposal. These provisions include, but are not limited to, proposed requirements relating to cold storage, separate physical storage, validation and setting specifications at the outer limits. Nevertheless, the FDA concerns covered by the proposed provisions are already being addressed by current industry practices.

IFC's comments include several suggested revisions that could allow manufacturers to continue to address these concerns with minimal change to current practice. This will avoid the unnecessary costs and potential compromises of quality of changing to a different practice where the desired end--protection of the public health-- is already being achieved. FDA's April announcement of the reopening of the comment period requested comments on the specific changes in current activities that would be required for companies to comply with proposal. This is difficult to summarize, although we have made reference to these activities throughout our comments.

More importantly, it is unnecessary and unduly burdensome to ask industry to spend the time necessary to itemize and estimate the cost of every activity that would have to change, when we can otherwise demonstrate that there is no need for a particular change. However, in an effort to be responsive to FDA's request, we have attempted under the relevant sections to qualitatively identify the relative cost impact of implementing activities that would have to change. It is important to recognize that safe high-quality formula is already being regularly manufactured under current regulations and manufacturing practices.

IFC states once again its strong view that an additional round of notice and comment is a necessary procedural step to effecting a defensible and appropriate final regulation. (Refer to II. Specific Objection to April 28, 2003 Notice.) If an additional round of notice and comments is not granted, the actual time needed to implement the provisions of the final rule will depend on the number of the significant proposed provisions which are adopted as

final regulations. In some instances, from six months to several years may be necessary.

Given the extent of the IFC's concerns over certain provisions, we are also troubled that the relatively short time given for comment on this complex regulation did not enable us to prepare comments that exhibit the depth of understanding and convey with clarity the needed changes to the proposal that the industry always strives to present in its comments to the Agency. As FDA is aware, the infant formula GMP proposal involves an extremely technical subject, impacts every facet of a complex manufacturing operation and contains numerous provisions that are interdependent. Because of the IFC's concern about the content and the effective date of the final regulation, we invite FDA to contact the IFC if any of the IFC's comments are unclear or not fully understood.

V. Overly Prescriptive/Inflexible Provisions

In our 1996 comments, we spoke of the Clinton Administration's "Reinventing Government" initiative to reduce the economic and other burdens of overly prescriptive or inflexible regulations. While that initiative no longer exists, per se, its spirit remains in full force, particularly with the current Administration's emphasis on accountability. Application of the spirits of both "Accountability" and "Reinventing Government" to good manufacturing practice regulations should dictate that FDA establish the results to be achieved in the infant formula manufacturing process, but not prescribe or limit the ways in which the required results can be achieved. Many provisions in the proposed regulation, unfortunately, are inflexible and overly prescriptive. In many instances, and without scientific justification, FDA's proposal mandates the use of only one method to prevent infant formula adulteration; alternative, equally effective, methods are not described, compared or permitted. Common sense, as well as Administrative guidance requires the least burdensome means of preventing adulteration, which would include allowing alternative methods of preventing adulteration. [See: Robert C. Gelardi's Oral Testimony before the FAC, April 4, 2002 (Attachment N)]

VI. "Specifications"

The effect of the proposed regulations is to require that the outer limits of acceptability be defined for multiple quality parameters and that specifications be set at those outer limits. They require in many places that materials exceeding these limits must be rejected. While this concept might initially appear to have merit to assure that infant formula is not distributed unless it is "within specifications," it does not withstand close scrutiny. It differs significantly from established control practices, and could lead to less tightly controlled production practices.

IFC members establish tight internal specifications, much tighter than the proposed outer acceptability limits. These tight specifications are intended to and operate to force the manufacturer's production controls to achieve a very consistent finished product. While the objective during manufacturing is to produce a product that falls within these tight internal specifications, the failure to do so does not necessarily mean that the product is in any way adulterated or unfit. Any result outside the tight, internal specifications triggers formal, documented review for material disposition decisions. A result outside of these tight

specifications, however, does not trigger automatic rejection, because these tight internal specifications are set far more narrowly than the outer acceptability limits.

The IFC believes that setting specifications as defined in the proposed regulation is ill advised for the following reasons:

a. Setting specifications at the outer acceptability limits would result in the widest possible specification bands. These bands would have very little meaning for day-to-day operations, because a manufacturer should be encouraged to control its manufacturing process tightly. A manufacturer who controlled its process only within outer limits could be expected to produce formulas of disturbingly variable quality.

b. Because infant formula manufacturers control processes and set specifications well within outer acceptability limits for most situations, they have not identified every outer limit for every process and product parameter that would result in rejection. Implementation of this outer acceptability limit approach with "documentation of the scientific basis for each standard or specification," as mentioned in the preamble, would require an overwhelming amount of technical and administrative resources and would require years of effort to complete. Even if these limits were finally obtained, their application would be questionable in complex, multi-factorial situations. A combination of individual results within the outer limits could form the basis of a rejection decision if reviewed critically, even though no specific outer acceptability limit was exceeded. Under the proposal's concept of specifications, however, that critical review would not necessarily occur. Therefore, it is much more protective to have tighter specification limits set, with mandatory documented reviews if they are not met, as is the current practice.

c. Setting tighter specifications than these outer acceptability limits is scientifically justified. Reviews for material acceptability beyond these tighter specification limits assure the proper assessment of each individual situation and serve to aid the manufacturer far better than having individual outer acceptability limits, which may not be useful in every case. In fact, IFC members establish even tighter "target values" within specifications where the operators will adjust the process if the range limit is exceeded. No documented review is necessary in situations where results are outside target values, as long as the measured parameters are still within current specifications. The approach of having target values within specifications, both of which are well within any outer acceptability limits, keeps the product and the process well centered, tightly controlled and consistent.

d. If the proposal is enacted, it would represent a significant expenditure in time and resources to identify outer limits for multiple quality parameters. Such effort would produce no additional quality benefits or consumer protection. In fact, operating within the outer acceptability limits contemplated by the proposal

> would probably have the undesirable result of manufacture of infant formulas with more variable nutrient content and quality characteristics. This is a direct contradiction of what a GMP regulation should promote.

Therefore, the IFC strongly recommends that the final regulation preserve the IFC members' current practice of target values (tight control ranges), coupled with a review and documentation requirement for deviations. These practices better serve the interest of achieving consistent high quality infant formulas. The comments throughout the remainder of this document reflect this recommended approach.

If, despite the IFC's urging, the Agency opts to establish the definition of "specification" at the outer acceptability limits, then it is strongly recommended that the manufacturers be allowed the alternative to retain the current tighter control range approach and to determine whether or not outer acceptability limits need to be established at each given step in the manufacturing process, as opposed to making the establishment of outer limits an absolute requirement in every case.

VII. Validation: Over-reliance on a "Drug" GMP Model

IFC previously commented in 1996 that FDA's proposal over-relied on CDER's drug GMP model as the basis for its proposed infant formula GMP regulation. Although the comment addressed many provisions in the drug GMPs that were incorporated in the proposed infant formula GMPs, the specific element focused upon in the 1996 IFC comments was validation.

It is significant in the context of CFSAN's 2003 reopening of the 1996 infant formula GMPs that seven years have passed and that CDER is in the process of implementing a significant examination and revaluation of its drug GMPs under an initiative known as "Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century: A Risk Based Approach." FDA summarized the initiative as follows:

> On August 21, 2002, FDA announced a major new initiative on the regulation of drug product quality. The two-year program, which applies to human drugs and biologics and veterinary drugs, has several ambitious objectives. One is to ensure that regulatory review and inspection policies are based on state-of-the-art pharmaceutical science and to encourage the adoption of new technological advances by the pharmaceutical industry. FDA will determine the best pathway to better integrate advances in quality management techniques, including quality systems approaches, into the Agency's regulatory standards and systems for the review and inspection processes. Additionally, risk-based approaches, that focus both industry and Agency attention on critical areas, will be implemented. Finally, enhancements to the consistency and coordination of Agency drug quality regulatory programs will be made. FDA Press Release (http://www.fda.gov/cder/gmp/21stcenturysummary.htm)

The IFC submits that FDA's current risk based drug GMP initiative may be a model from which infant formula GMPs may benefit. The IFC suggests that the infant formula

industry partner with CFSAN, in much the same way that CDER, CBER and CVM are partnering with the industries they regulate to arrive at risk-based GMPs that accomplish the objectives of "Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century: A Risk Based Approach."

The balance of this general comment will, like the IFC's 1996 comment, focus on the validation requirements of the reopened proposal. The IFC's 1996 comments stated that the validation section in proposed section 106.35 was so vague and the impact so enormous that implementing it, without engaging the efforts of an extensive interactive task force (composed of both industry and FDA personnel) would be unwise. In proposed section 106.35(a)(4) the Agency proposed that, for purposes of the section, "validation" means establishing documented evidence that provides a high degree of assurance that a system will consistently produce a product meeting its predetermined specifications and quality characteristics. In proposed section 106.35(b)(1), FDA proposed that all automatic systems be designed, installed, tested, and maintained in a manner that will ensure that they are capable of performing their intended function. While these provisions are capable of an interpretation appropriate to infant formula, they are also capable of an interpretation more appropriate to pharmaceutical manufacture. In the absence of some assurance to the contrary, IFC was concerned that an inappropriate drug-style interpretation might prevail.

It is imperative that drugs contain the precise amount of active ingredient to achieve efficacy in treating illness. Moreover, most "drugs," even if manufactured properly, are potentially toxic. Therefore, because their margin of safety can be so critical, their manufacture requires far more critical tolerances than do infant formulas. Accordingly, it is important not blindly to take the historic "drug" approach in proposing regulations for infant formula. For instance, requiring strict "drug-like" validation and revalidation of systems used to manufacture infant formula would be extremely costly, unnecessarily burdensome and a disincentive for process improvements (i.e., improvements may not be implemented simply because of the burden of complex re-validation).

One of the purposes of systems validation is to lessen the need to rely on finished product testing to establish the acceptability of the finished product as stated in the May, 1987 Guideline on General Principles of Process Validation: "Successfully validating a process may reduce the dependence upon intensive in process and finished product testing." But, lessening of testing does not justify validation of systems used to manufacture infant formulas, because validation will not lessen the extensive, legally mandated testing burden for infant formula. The nutrient content of infant formulas is mandated by the Infant Formula Act, as is testing for each of those mandated nutrients in each batch of infant formulas (by validated methods if the IFC's comments to proposed 106.91(a)(4) are accepted). Thus, compliance of infant formulas with the required nutrient levels is currently achieved without the imposition of extensive drug-like validation requirements, and extensive validation requirements will provide no greater assurance of compliance.

The Agency has proposed an all-encompassing definition of "validation." As seen in the pharmaceutical industry, excessive validation requirements forced manufacturers to minimize process improvements and quality and product innovations. If applied to infant

formula manufacturers, it would result in substantial lost capacity and may close the doors to many potential new manufacturers. This degree of validation is well beyond the scope that has been applied even in the drug industry. It would cost many millions of dollars to accomplish and would require a time frame to achieve compliance measured in years. Neither the industry nor consumers are ready for such an exhaustive and unwarranted burden, which would entail significant additional costs to infant formula manufacturing without any additional consumer protection.

Contrasted to the manufacture of drugs, which involves relatively simple formulations and processes, infant formula manufacturing involves several times the number of pieces of equipment and software to produce the finished product. Thus, applying drug-type validation requirements on the infant formula industry will have a very heavy cost impact. This is contrary to one of the purposes of the regulations stated by the Agency in the preamble -- to allow potential new competition, without huge, burdensome financial impact.

Having carefully considered the industry's experience over the last 7 years with validated processes and systems, IFC has refined its thinking on the proposed requirements. The industry remains of the view that the indiscriminate and across-the-board requirement of validation is inappropriate. Nevertheless, IFC clearly recognizes that validation of critical systems can be a valuable quality assurance tool for the infant formula manufacturer. Infant formula manufacturers are already validating systems and procedures based upon a risk-based criticality assessment. IFC believes that the Agency should recognize and accept a tiered approach to validation including such other concepts as verification, qualification, capability studies, challenge testing, and operational testing. For example, HACCP involves both risk-based criticality assessment and other documented levels of control. Each company should decide the levels of validation required, based upon the degree of criticality of each system to assuring the safety and quality of the infant formula produced. The Agency's April announcement of the reopening of the comment period asked how often manufacturers validate their systems. It is impossible to respond to this in any quantified manner, but it can be said that systems that manufacturers deem critical are revalidated whenever they undergo any significant change.

Manufacturers may use a variety of qualification and validation processes prior to release of commercial product to assure that systems and procedures can produce acceptable quality product on an ongoing basis. ("Acceptable quality" product is that product that meets manufacturer specifications and the requirements of the FFDCA). These activities identify the systems involved in the manufacture of a given infant formula product and characterize the criticality of each system based on its potential for product impact. Using specifications and quality characteristics, test plans based on the categorized systems are developed, testing is completed, results are documented, and commercial product release is based on compliance. Changes or modifications to the existing qualified systems and validated processes occur following a formal documented review of the proposed changes to establish potential product impact and to respond with the appropriate validation activity.

The Agency also proposed in 1996 that systems be validated before their first use to manufacture commercial product. IFC believes that this aspect of the provision is overly

stringent, since any product produced during a validation run that met release criteria should be eligible for commercial release. As proposed, the rule would arbitrarily and capriciously require that whole batches of infant formula, worth up to hundreds of thousands of dollars each, be produced solely for validation purposes, only to be discarded. The cost impact across the industry of this aspect of the rule would be huge. Even in the rigid world of drug validation, "concurrent validation" is accepted by the Agency and would allow for the release of validation batches that otherwise met release criteria.

As we stated in our 1996 comments, the validation section is "so vague, as presently proposed, and the impact is so enormous that implementing 106.35 would be counterproductive unless significant further dialogue with the Agency to acquire a mutual understanding of this concept takes place." Therefore, if the Agency persists in its belief that validation should be employed by the infant formula industry, the IFC recommends that the Agency and the industry form a working task force to define the scope and content of risk-based systems validation for infant formula. Such definitions would be limited to hardware and software for applications that are critical to the manufacture of infant formula, and would exclude non-critical systems. Through such a task force, the Agency will be able to assess the cost impact and the degree of industry resources and time necessary to attain compliance. This type of cooperative approach involving a working team of FDA and industry representatives has been previously employed for Low Acid Canned Food matters and for the current 1986 Guidelines, and would be appropriate in this subject area as well.

VIII. Recordkeeping: The Regulation Should Focus on "Necessary" Documents

The proposed documentation requirements are very burdensome. They would certainly necessitate additional staffing to implement, but it is difficult to quantify this cost without further clarification. Similarly, it is not possible to comment further on the estimated annual recordkeeping burden until these regulations are finalized.

However, the IFC believes the required records should be limited overall to focus on and incorporate the statutory reference to "necessary" documents, rather than the broad "including but not limited to" language of the proposal. The IFC's suggested revisions reflect this approach. Also, the IFC recommends that the final regulation reflect the acceptability of electronic recordkeeping.

IX. Proposed Definition of "Manufacturer"

The proposed definition of "manufacturer" will result in multiple and overlapping responsibilities, recordkeeping, and notifications to FDA whenever co-packers are involved in the manufacture of infant formula. The IFC does not believe that duplicate responsibilities for the same activity serve any purpose in the majority of proposed requirements, and suggests that the concept of "responsible party" be introduced to eliminate duplication. If the IFC's recommendations are accepted, for certain requirements, the responsible party will replace the manufacturer completely, in order to avoid duplication and to fix actual responsibility appropriately. For other requirements, the responsible party is suggested as a possible alternative to the manufacturer, so that the parties involved may decide what is appropriate.

For the purpose of "registration," alone, IFC believes that it will serve FDA's purpose (e.g., inspections and counterfeit formula surveillance) to require registration by all parties involved in any aspect of infant formula manufacturing.

X. Notification of "Adulteration" or "Misbranding"

A violation of the final infant formula GMP, no matter how minor or inconsequential, will constitute a "technical adulteration or misbranding" of the product. In turn, adulteration and misbranding of products potentially triggers FDA's full enforcement arsenal. While FDA's enforcement discretion can temper the deployment of this arsenal, unique provisions of the law applicable only to infant formula require close examination. In the realm of food providers, infant formula manufacturers alone are required to notify FDA when distributed products are "adulterated" or "misbranded." Thus, it is critical to weigh each proposed regulation for the consequences of a finding of "adulteration" or "misbranding" to ensure that they are appropriate.

Key to the appropriate application of infant formula GMPs is that only a finding of the type of adulteration of significance to public health should trigger a given consequence. Likewise, only significant or actionable misbranding situations should trigger notification. Thus, when the 1986 amendments were enacted, Senator Hatch stated that "technical violations" should not trigger notification or recall:

> "We didn't feel that notification or recalls should be required in all cases which might constitute a technical adulteration or misbranding, but, rather, felt that an actual rather than theoretical risk to human health must exist...." (Cong. Record -- Senate, Sept. 27, 1986, p. S14047)

Echoing Senator Hatch, Senator Metzenbaum said that it was not the intention of Congress:

> "that formula be deemed adulterated or that the submission requirement ... or the notification requirement ... be triggered by violations such as clerical lapses, unless of course they are of such a nature as may affect the quality or content of the formula." (Id. at S14046).

Senator Metzenbaum concluded by directing FDA to distinguish one variety of violation from the other in regulations or guidelines. It is important for the final GMP regulations to reflect this legislative intent so that minor, technical violations do not trigger frequent notifications when the quality or content of infant formula is not conceivably compromised.

XI. Redundancy

Another objective of "Reinventing Government" that the current Administration has apparently ratified is to reduce the number of redundant and/or meaningless regulations.

Numerous activities proscribed or mandated by the proposed infant formula GMPs are already proscribed or mandated by the current Food GMPs and/or other existing FDA regulations. These include personnel requirements, and the permitted use of food ingredients and food-contact materials. Such redundancies do not provide the public with any greater protection. They serve only to create unnecessary confusion in those plants manufacturing both infant formulas and similar products not intended for use by infants, at the same time that they contravene Administrative guidance.

FDA's specific stated intent in promulgating the Food GMPs was to have those regulations function as "umbrella" regulations. Additional regulations, targeted at specific industries, were contemplated under the Food GMP umbrella. (See 51 F.R. 22459 (June 19, 1986), comment 3) Consistent with this expressed intention, and to avoid duplication consistent with President Clinton's mandate, we recommend that any duplicate requirements be eliminated from the infant formula GMP regulations. The public may rest assured that infant formula manufacturers are already sufficiently guided by the presence of these provisions under the Food GMP umbrella regulations.

XII. Infant Formula Submission Review by FDA

IFC also wishes to express the need for FDA to establish and make known a well-defined, transparent and practical process for the receipt, review and disposition of various submissions from industry. Such an agency process needs to have clearly defined aspects, such as time lines, how a submission is reviewed and by whom, and, importantly, a response and dialogue process with the submitter in addressing Agency interests. This process is necessary for ethical industry to be able to plan and implement infant formula advancements in a reasonable and mutually cooperative manner.

The Agency has made significant strides in providing acknowledgment letters in a timely manner, in identifying an appropriate contact for follow-up questions on a given submission, and in overcoming their previous reluctance to discuss submissions while they are under review. More progress is needed in most of these areas, however, and also in providing greater clarification, as to which types of substantive additions to a submission will cause the 90-day clock to start ticking all over again, versus which will be considered helpful in completing the initial review within the statutory time period.

XIII. FDA's Means to Assure the Safety and Availability of New and Improved Infant Formulas -- Premarket Notification Not Premarket Approval

FDA and infant formula manufacturers share the responsibility of carrying out the intention of Congress to assure that new and improved infant formulas reach the public expeditiously. Congress was clear that it envisioned premarket notifications to FDA, but not a premarket approval process:

> "When Mr. Metzenbaum's earlier amendment was approved by the Senate, it contained a provision which would have required a premarket approval by the

> Secretary for new or altered formulas. The FDA has since made a strong case that a premarket approval is not desirable in this instance. FDA points out that the burden to produce a safe and effective formula should remain squarely on the shoulders of the manufacturer." (Congressional Record -- Senate, September 27, 1986, p. S14046)

Consistently, Mr. Hatch stated the following on the record:

> "I also agree with the FDA that premarket approval is not desirable in this instance and understand that the [notification] procedure is not intended to become a precursor of such FDA action." (*Id.* at S14047)

Thus, the notification requirement was intended by Congress as a means of assuring consumers a reasonable standard of safety while not unreasonably burdening the industry through a potentially cumbersome system of premarket clearance. [See: Senate Committee on Labor and Human Resources Report, No.96-916: The Infant Formula Act, p.6]

There are several provisions in the GMP proposal that exceed the premarket notification structure intended by Congress when it enacted the 1986 Infant Formula Act Amendments.

The Framers of the Infant Formula Act intended the line between premarket notification and premarket approval to be bright. To this end, Congress took the extraordinary, in fact unique, step to develop and codify nutrient specifications. For formulas, FDA's role in the premarket notification process was perceived by Congress as comprising the task of confirming that the required specifications are met for each new or significantly modified formula.

To ensure that this important review function did not evolve into a premarket approval evaluation, Congress channeled the Agency's substantive authority under section 412 to apply only to those elements necessary to ensure that a Syntex/NeoMulsoy nutrient deficiency scenario never occurs again. Over the years, the practices and procedures FDA has followed in reviewing section 412 notifications have consistently taken on more and more of the trappings of premarket approval systems quite different from the limited, precise review function contemplated in the statutory scheme.

FDA has so proceeded even though, Congress, when it amended the Infant Formula Act in 1986, rejected premarket approval for infant formulas. Instead, in order to assure the nutritional integrity of infant formula, Congress granted FDA express authority to enact GMPs, require record development and maintenance, and impose in-process controls. All of these requirements were designed to help ensure the nutritional quality of formula and, thus, avoid the marketing of a nutrient-deficient formula. Tellingly, the resulting statutory scheme carefully avoids any form of preclearance or premarket approval role for FDA and, instead, focuses on the role of 1) establishing standards and practices manufacturers must follow and 2) documenting compliance. As FDA approaches accomplishing the statutory goal of enacting workable GMP requirements and, in the process, enhancing the nutritional quality of formulas, it commensurately must turn its attention to revising its practices to

better achieve the statute's goal of premarket notification bereft of unauthorized and unwarranted premarket approval attributes.

IFC'S SPECIFIC COMMENTS TO FDA'S PROPOSAL

FDA Proposed Regulation	IFC Suggested Language
Part 106--INFANT FORMULA--REQUIREMENTS PERTAINING TO CURRENT GOOD MANUFACTURING PRACTICE, QUALITY CONTROL PROCEDURES, QUALITY FACTORS, RECORDS AND REPORTS, AND NOTIFICATION	**Part 106--INFANT FORMULA--REQUIREMENTS PERTAINING TO CURRENT GOOD MANUFACTURING PRACTICE, QUALITY CONTROL PROCEDURES, QUALITY FACTORS, RECORDS AND REPORTS, AND NOTIFICATION**
106.1 Status and applicability of the regulations in part 106.	**106.1 Status and applicability of the regulations in part 106.**
106.1(a) The criteria set forth in subparts B, C, and D of this part prescribe the steps that manufacturers must take under section 412(b)(2) and (b)(3) of the Federal Food, Drug, and Cosmetic Act (the act) in processing infant formula. If the processing of the formula does not comply with any regulation in subparts B, C, or D of this part, the formula will be deemed to be adulterated under section 412(a)(3) of the act.	Acceptable as proposed.
106.1(b) The criteria set forth in subpart E of this part prescribe the quality factor requirements that infant formula must meet under section 412(b)(1) of the act. If the formula fails to comply with any regulation in subpart E of this part, it will be deemed to be adulterated under section 412(a)(2) of the act.	Acceptable as proposed.
106.1(c) The criteria set forth in subpart F of this part implement the record retention requirements established in section 412(b)(4) of the act. Failure to comply with any regulation in subpart F of this part is a violation of section 301(e) of the act.	Acceptable as proposed.
106.1(d) The criteria set forth in subpart G of this part describe the circumstances in which infant formula manufacturers are required to register with, submit to, or notify the Food and Drug Administration, and the content of those registrations, submissions, or notifications, under section 412(c), (d), and (e) of the act. Failure to comply with any regulation in subpart G of this part is a violation of section 301(s) of the act.	Acceptable as proposed.

FDA Proposed Regulation	IFC Suggested Language
106.3 Definitions. 106.3(a) Batch means a specific quantity of an infant formula or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.	**106.3 Definitions.** 106.3(a) Batch means a specific quantity of an infant formula that is intended to have uniform composition, character and quality, and is produced according to a master manufacturing order during the same cycle of manufacture.

IFC Redlined Version

106.3(a) Batch means a specific quantity of an infant formula ~~or other material~~ that is intended to have uniform composition, character and quality, ~~within specified limits~~, and is produced according to a master ~~single~~ manufacturing order during the same cycle of manufacture.

IFC Comment

IFC is unsure what is meant by "or other material" in the context of this proposal and has suggested striking it from the definition of batch, but using it in the definition of "lot" in 106.3(g) and (h). The word "composition" adds to the accepted concept of the characteristics of a batch.

See the IFC's General Comment concerning Specifications for the rationale to strike "within specified limits." In addition to the rationale in that General Comment, the phrase creates a substantive requirement that could cause confusion if contained in a definition. Whether a batch meets specified limits relates to the disposition of the batch (as a substantive matter), not to whether it is a batch (a definitional matter). Currently Specifications for products are set based on research and clinical studies. Because infant formula manufacturers control processes and set specifications well inside outer acceptability limits for most situations, they have not identified every outer limit for every process and product parameter that would result in rejection. Implementation of this outer acceptability limit approach with "documentation of the scientific basis for each standard or specification," as mentioned in the preamble, would require an overwhelming amount of technical and administrative resources and would require years of effort to complete. Extensive resources would be needed for additional personnel for research, analytical testing and manufacturing to evaluate each new product to the limits of acceptability. This would have a large impact on resources and would not provide any additional safety factor for the consumer. Additionally, if each specification needs to be tested to failure, the cost would prevent or severely limit new product development. Moreover, even if these limits of acceptability were identified, their application would be questionable in complex, multi-factorial situations. That such a requirement is unnecessary can be seen by the fact that current formulation policy and release procedures required by regulation ensure the release of product that routinely meets infant formula standards.

Finally, the IFC has suggested changing "single" to "master." The definition should not suggest that a manufacturing order for in-process adjustments, undertaken so that the batch meets nutritional requirements, might contravene the definition.

FDA Proposed Regulation	IFC Suggested Language
106.3(b) Final-product-stage means the point in the manufacturing process, before distribution of an infant formula, at which the infant formula is homogeneous and is not subject to further degradation due to processing	Acceptable as proposed.
106.3(c) Indicator nutrient means a nutrient whose concentration is measured during the manufacture of an infant formula to confirm complete addition and uniform distribution of a premix or other substance of which the indicator nutrient is a part.	Acceptable as proposed.
106.3(d) Infant means a person not more than 12 months of age.	Acceptable as proposed.
106.3(e) Infant formula means a food which purports to be or is represented for special dietary use solely as a food for infants by reason of its simulation of human milk or its suitability as a complete or partial substitute for human milk.	Acceptable as proposed.
106.3(f) In-process batch means a combination of ingredients at any point in the manufacturing process before packaging.	Acceptable as proposed.
106.3(g) Lot means a batch, or a specifically identified portion of a batch, having uniform character and quality within specified limits; or, in the case of an infant formula produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.	106.3(g) Lot means a batch, a specifically identified portion of a batch, or other material having uniform composition, character and quality; or, in the case of an infant formula produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform composition, character and quality.

IFC Redlined Version

106.3(g) Lot means a batch, ~~or~~ a specifically identified portion of a batch, or other material having uniform composition, character and quality ~~within specified limits~~; or, in the case of an infant formula produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform composition, character and quality ~~within specified limits~~.

IFC Comment

See the IFC's Specific Comment to proposed 106.3(a). The IFC believes that the

phrase "or other material" in this definition encompasses raw material lots, etc. better than it does in the definition of "batch."

FDA Proposed Regulation	IFC Suggested Language
106.3(h) Lot number, control number, or batch number means any distinctive combination of letters, numbers, symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of infant formula or other material can be determined.	Acceptable as proposed.
106.3(i) Major change in an infant formula means any new formulation, or any change of ingredients or processes where experience or theory would predict a possible significant adverse impact on levels of nutrients or bioavailability of nutrients, or any change that causes an infant formula to differ fundamentally in processing or in composition from any previous formulation produced by the manufacturer. Examples of infant formulas deemed to differ fundamentally in processing or in composition include:	Acceptable as proposed.
106.3(i)(1) Any infant formula produced by a manufacturer who is entering the U.S. market;	Acceptable as proposed.
106.3(i)(2) Any infant formula powder processed and introduced for commercial or charitable distribution by a manufacturer who previously only produced liquids (or vice versa);	Acceptable as proposed.
106.3(i)(3) Any infant formula having a significant revision, addition, or substitution of a macronutrient (i.e., protein, fat, or carbohydrate), with which the manufacturer has not had previous experience;	Acceptable as proposed.
106.3(i)(4) Any infant formula manufactured on a new processing line or in a new plant;	Acceptable as proposed.
106.3(i)(5) Any infant formula manufactured containing a new constituent not listed in section 412(i) of the act, such as taurine or L-carnitine;	106.3(i)(5) Any infant formula manufactured containing a new nutrient not listed in section 412(i) of the act, such as taurine or L-carnitine;

IFC Redlined Version

106.3(i)(5) Any infant formula manufactured containing a new nutrient ~~constituent~~ not listed in section 412(i) of the act, such as taurine or L-carnitine;

IFC Comment

We believe that the use of the term "nutrient" is much more consistent with the purpose of the Infant Formula Act: the assurance of proper nutrition. The Agency's proposed language, "new constituent," opens the scope of section 412. "New constituent" is clearly overbroad and could render, as a major change, a wholly and harmless innocuous new

constituent at nominal levels and, furthermore, is beyond the basic scope of Section 412: The Assurance of Nutritional Adequacy.

Additionally, FDA's April announcement of the reopening of the comment period requested comments on the specific changes in current activities that would be required for companies to comply with the proposal. Infant formula manufacturers currently provide a submission when a new nutrient is added to the product. If the new regulations require that any new constituent renders a formulation a "new formula" or "major change", this would significantly increase the number of filings that would need to be developed – each requiring a 90-day review period. This would result in additional resources being expended at both the manufacturer and within FDA with no added benefit to the consumer.

The term "constituent" alone is problematic, as it could make a "major change" of what would truly be a "minor change" (e.g., a change in emulsifier). The phrase suggested by the IFC eliminates this potential result, while continuing to convey the examples listed by FDA in the proposed language.

FDA Proposed Regulation	IFC Suggested Language
106.3(i)(6) Any infant formula processed by a manufacturer on new equipment that utilizes a new technology or principle (e.g., a change from terminal sterilization to aseptic processing); and	Acceptable as proposed.
106.3(i)(7) An infant formula for which there has been a fundamental change in the type of packaging used (e.g., changing from metal cans to plastic pouches).	Acceptable as proposed.

FDA Proposed Regulation	IFC Suggested Language
None.	106.3(j) Minor change in an infant formula means any new formulation, or any change of ingredients or processes where experience or theory would not predict a possible significant adverse impact on nutrient levels or nutrient availability. Minor changes may or may not affect whether a formula is adulterated under section 412(a) of the Act; changes that affect whether a formula is adulterated under section 412(a) of the Act would require the manufacturer to notify FDA prior to first processing.
	106.3(j)(1) Examples of minor changes to infant formulas that require notification prior to first processing include:
	106.3(j)(1)(i) Reduction of a nutrient that results in a label change, change in a nutrient level which is within 10% of the nutrient levels, minimum or maximum required by Section 412(g) of the FFDCA and is at least 10% closer to the required level;
	106.3(j)(1)(ii) Any change in the identity of the

	ingredients providing nutrients required under section 412 (g) of the Act or trace nutrients added voluntarily consistent with 21 CFR 107.10(b)(5);
	106.3(j)(1)(iii) Any design change in the formulation or processing of an infant formula which the manufacturer determines calls for non-routine nutrient testing prior to release, for the purpose of determining whether a possible change has occurred in the levels of nutrients in meeting requirements of Section 412(g) of the Act.
	106.3(j)(2) Examples of minor changes to infant formulas that do not require notification prior to first processing include:
	106.3(j)(2)(i) Minor reduction of iron level;
	106.3(j)(2)(ii) Replacing certain nutrient forms with another form;
	106.3(j)(2)(iii) Adjustments in the quantity of a nutrient in a premix or individually added nutrient that results in a specification change for that nutrient in the finished product;
	106.3(j)(2)(iv) Changes in time-temperature conditions of preheating during handling of bulk product that cannot reasonably be expected to cause an adverse impact on nutrient levels or nutrient availability;
	106.3(j)(2)(v) Changes in oxygen content of a packaged product that might have minimal effect on the level of nutrients.

IFC Redlined Version

106.3(j) Minor change in an infant formula means any new formulation, or any change of ingredients or processes where experience or theory would not predict a possible significant adverse impact on nutrient levels or nutrient availability. Minor changes may or may not affect whether a formula is adulterated under section 412(a) of the Act; changes that affect whether a formula is adulterated under section 412(a) of the Act would require the manufacturer to notify FDA prior to first processing.

106.3(j)(1) Examples of minor changes to infant formulas include:

106.3(j)(1)(i) Reduction of a nutrient that results in a label change, change in a nutrient level which is within 10% of the nutrient levels, minimum or maximum required by Section 412(g) of the FFDCA and is at least 10% closer to the required level;
106.3(j)(1)(ii) Any change in the identity of the ingredients providing nutrients required under section 412 (g) of the Act or trace nutrients added voluntarily consistent with 21 CFR 107.10(b)(5);

106.3(j)(1)(iii) Any design change in the formulation or processing of an infant formula

which the manufacturer determines calls for non-routine nutrient testing prior to release, for the purpose of determining whether a possible change has occurred in the levels of nutrients in meeting requirements of Section 412(g) of the Act.

106.3(j)(2) Examples of minor changes to infant formulas that do not require notification prior to first processing include:

106.3(j)(2)(i) Minor reduction of iron level;

106.3(j)(2)(ii) Replacing certain nutrient forms with another form;

106.3(j)(2)(iii) Adjustments in the quantity of a nutrient in a premix or individually added nutrient that results in a specification change for that nutrient in the finished product;

106.3(j)(2)(iv) Changes in time-temperature conditions of preheating during handling of bulk product that cannot reasonably be expected to cause an adverse impact on nutrient levels or nutrient availability;

106.3(j)(2)(v) Changes in oxygen content of a packaged product that might have a minimal effect on the level of nutrients.

IFC Comment

The 1996 Proposal omitted any mention of "minor change." The current regulations, however, define "minor change" in 21 CFR 106.30(c)(1) as follows:

> A minor change is a minor reduction in nutrient levels, a minor increase in levels of nutrients that are subject to maximum limits established under section 412(g) of the Act or in regulations established under section 413(a)2) of the Act, or any other change where experience or theory would not predict a possible significant adverse impact on nutrient levels or nutrient availability. After a minor change the manufacturer shall analyze representative samples for all nutrients so changed and those possibly affected by the change.

In addition to this definition, FDA years ago issued guidance (currently available on the Agency's website) that the industry has routinely followed in assessing whether a change is major or minor. By omitting the minor change concept entirely, the 1996 proposal produced unnecessary confusion on the part of industry and, we believe, has resulted in inconsistent positions on the part of the Agency regarding the factors and considerations that govern a determination of whether and when a notification required under the Infant Formula Act must be submitted. The definition of "minor change" suggested above incorporates the concepts articulated by the FDA in its 1986 Guidelines. The definition will provide needed clarification.

FDA Proposed Regulation	IFC Suggested Language
106.3(j) Manufacturer means a person who prepares, reconstitutes, or otherwise changes the physical or chemical characteristics of an infant formula or packages or labels the product in a container for distribution.	Acceptable; Renumbered as 106.3(k).
106.3(k) Microorganisms means yeasts, molds, bacteria, and viruses and includes, but is not limited to, species having public health significance.	Delete.

IFC Redlined Version

106.3(jk) Manufacturer means a person who prepares, reconstitutes, or otherwise changes the physical or chemical characteristics of an infant formula or packages or labels the product in a container for distribution.

~~106.3(k) Microorganisms means yeasts, molds, bacteria, and viruses and includes, but is not limited to, species having public health significance.~~

IFC Comment

See the IFC's General Comment regarding Redundancy. This definition of "Microorganisms" is identical to the definition in the Food GMPs (110.3(i)), which are also applicable to the manufacture of infant formulas.

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FDA Proposed Regulation	IFC Suggested Language
106.3(l) New infant formula means: (1) An infant formula manufactured by a person that has not previously manufactured an infant formula for the U.S. market, and (2) An infant formula manufactured by a person that has previously manufactured infant formula and in which there is a major change in processing or formulation from a current or any previous formulation produced by such manufacturer.	Acceptable as proposed. Acceptable as proposed. Acceptable as proposed.
106.3(m) Nutrient means any vitamin, mineral, or other substance or ingredient that is required in accordance with the table set out in section 412(i)(1) of the act or by regulations issued under section 412(i)(2) or that is identified as essential for infants by the Food and Nutrition Board of the National Research Council through its development of a Recommended Dietary Allowance or an Estimated Safe and Adequate Daily Dietary Intake range, or that has been identified as essential for infants by the Food and Drug Administration through a Federal Register publication.	106.3(m) Required nutrient means any vitamin, mineral, or other substance or ingredient in infant formula that is required by the act or by regulations issued pursuant to the act.

IFC Redlined Version

106.3(m) Required ~~N~~nutrient means any vitamin, mineral, or other substance or ingredient in infant formula that is required ~~in accordance with the table set out in section 412(i)(1) of~~ by the act or by regulations issued ~~under section 412(i)(2) or that is identified as essential for infants by the Food and Nutrition Board of the National Research Council through its development of a Recommended Dietary Allowance or an Estimated Safe and Adequate Daily Dietary Intake range, or that has been identified as essential for infants by the Food and Drug Administration through a Federal Register publication~~ pursuant to the act.

IFC Comment

The IFC believes that the intention of the proposal is to describe the ways in which new required nutrients can be added to the list of those already required by the nutrient table. The changes suggested by the IFC are intended to simplify the proposed language. For instance, the IFC was confused by the third point of this definition ("identified ... in a Federal Register publication") and if and how it related to the first point (a regulation issued under 412(i)(2)). If this third point were interpreted to cover Federal Register publications that did not constitute rulemaking, the IFC feels that it would be confusingly vague. To eliminate this interpretational confusion, the IFC suggests broadening the first point so that it encompasses all FDA rulemaking activities related to infant formula and eliminating the last clause of the proposal. Finally, although the IFC has the utmost respect for the NRC development of RDA's, the IFC does not believe that the Infant Formula Act gives FDA the authority to sub-delegate its authority to establish required infant formula nutrients and

levels.

The IFC interprets both the proposed language and its suggested revisions as applying to "essential" nutrients, and not to other potential or current ingredients in infant formula. In other words, the regulations will create no restrictions on the ability of a manufacturer to include new ingredients (assuming compliance with other provisions in the regulations), nor do they in any way affect substances that are being added currently in compliance with existing regulations.

FDA Proposed Regulation	IFC Suggested Language
106.3(n) Nutrient premix means a combination of ingredients containing two or more nutrients received from a supplier or prepared by an infant formula manufacturer.	Acceptable as proposed.
106.3(o) Quality factors mean those factors necessary to demonstrate that the infant formula, as prepared for market, provides nutrients in a form that is bioavailable and safe as shown by evidence that demonstrates that the formula supports healthy growth when fed as a sole source of nutrition.	106.3(o) Quality factors mean those factors necessary to demonstrate the bioavailability of a nutrient and the maintenance of level or potency of nutrients through an expected shelf life of the product.

IFC Redlined Version

106.3(o) Quality factors mean those factors necessary to demonstrate the bioavailability of a nutrient and the maintenance of level or potency of nutrients through an expected shelf life of the product ~~that the infant formula, as prepared for market, provides nutrients in a form that is bioavailable and safe as shown by evidence that demonstrates that the formula supports healthy growth when fed as a sole source of nutrition~~.

IFC Comment

As discussed at length in our general comments, IFC is strongly of the view that any effort to establish "healthy" or "normal" growth as a quality factor is flawed and should be abandoned. We specifically incorporate by reference those comments in support of the above noted recommended deletions from this proposed section.

We would delete the gratuitous reference to safety in the proposed definition to be consistent with the fact that, as discussed in our General Comments, the Infant Formula Act does not deal with "safety" per se, but rather with nutritional adequacy. This is also consistent with the fact that the Food Drug and Cosmetic Act *does* ensure safety in many ways. Consequently, the additional regulation dictated by the Infant Formula Act was only needed to focus on the particular reliance of infants on the nutritional aspects of a food that might substitute for breast milk as their sole source of nutrition.

We would also separate out the reference to evidence of growth because bioavailability might be established in many ways other than by a clinical trial. As discussed in our General Comment section on "Assessment of Normal Growth," such evidence should

not be considered a "Quality Factor" per se, nor should it be expected on a routine basis. Moreover, as was clear from the 2002 Food Advisory Committee discussions held to better understand how to assess growth, the task of defining "normal physical growth," which already appears in several of the proposed regulations – let alone "healthy growth," which is used here – is an elusive one, given the wide range of acceptable growth patterns exhibited by infants of different ages, genders, ethnic origins and feeding practices. IFC believes that "expected physical growth" is a more meaningful term and a more measurable criterion, since it may be established by comparison to the ranges used in whichever of the various, currently accepted, credible medical references may be most appropriate. Consequently, we suggest that the term be changed wherever it appears throughout the proposed GMPs.

FDA Proposed Regulation	IFC Suggested Language
106.3(p) Representative sample means a sample that consists of a number of units that are drawn based on rational criteria, such as random sampling, and intended to ensure that the sample accurately portrays the material being sampled.	Acceptable as proposed.
106.3(q) Shall is used to state mandatory requirements.	Acceptable as proposed.
106.3(r) Should is used to state recommended or advisory procedures or to identify recommended equipment.	Acceptable as proposed.
None.	106.3(s) Responsible party means the manufacturer of an infant formula when all manufacturing steps are performed by a single entity; however, when several entities are involved in the manufacture of a given formula, it means the manufacturer or other entity that has agreed to assume responsibility for ensuring that all requirements for notification and/or assurance under these regulations are satisfied.

IFC Redlined Version

106.3(s) Responsible party means the manufacturer of an infant formula when all manufacturing steps are performed by a single entity; however, when several entities are involved in the manufacture of a given formula, it means the manufacturer or other entity that has agreed to assume responsibility for ensuring that all requirements for notification and/or assurance under these regulations are satisfied.

IFC Comment

See the IFC General Comment regarding Definition of Manufacturer. The IFC does not believe that FDA needs or wants to receive multiple notifications conveying identical information or to saddle multiple manufacturers of the same formula with duplicative responsibilities for the same task. Such duplication could be required under the proposed regulations when two or more manufacturers are involved in the manufacture of an infant formula. Therefore, introduction of the concept of "Responsible Party" permits multiple manufacturers to agree in advance who will bear the various responsibilities. It should be

clear, however, that all manufacturers must register, i.e., they cannot avoid registration by virtue of the concept of Responsible Party.

FDA Proposed Regulation	IFC Suggested Language
None.	106.3(t) Specifications means quality control limits or standards for raw materials, in-process materials and finished product, which are established by the manufacturer for purposes of controlling quality and consistency for infant formula. Failure to meet an established specification requires a documented review and material disposition decision. 106.3(u) Target Value means quality control limits or standards for raw materials, in-process materials and finished product which are established by the manufacturer for purposes of targeting the manufacturing process to a tight range within broader specifications. Failure to meet an established target value shall result in an immediate review and adjustment, if necessary, during the manufacturing process. No documented review and material disposition is needed when a target value is not met, as long as the established specification is met.

IFC Redlined Version

106.3(t) Specifications means quality control limits or standards for raw materials, in-process materials and finished product, which are established by the manufacturer for purposes of controlling quality and consistency for infant formula. Failure to meet an established specification requires a documented review and material disposition decision.

106.3(u) Target Value means quality control limits or standards for raw materials, in-process materials and finished product which are established by the manufacturer for purposes of targeting the manufacturing process to a tight range within broader specifications. Failure to meet an established target value shall result in an immediate review and adjustment, if necessary, during the manufacturing process. No documented review and material disposition is needed when a target value is not met, as long as the established specification is met.

IFC Comment

See the IFC's General Comment concerning Specifications. In the drug industry, there is common acceptance that the term "specification" means a predetermined value or range for a given parameter. That parameter must be met in order routinely to continue the manufacturing process or to release the product for distribution. Failure to meet a specification triggers special, non-routine, documented review, not automatic rejection of the product. This is appropriate because the specifications, like those in the manufacture of infant formula, are set well within the outer limits that would cause adulteration. In view of

the IFC's definition of "Specification," the IFC has suggested deleting the word "standard" whenever it appears with the word "Specification" in FDA's proposed language.

The term "target value" should also be defined, not for purposes of requiring them, but instead to recognize that some infant formula manufacturers use them for quality control purposes. When they are used, it is important that they be distinguished from specifications, because the failure to meet a target value should not trigger the kind of detailed and documented review triggered by a failure to meet specifications.

FDA Proposed Regulation	IFC Suggested Language
None.	106.3(v) Critical is used to describe systems or equipment that have been designated by the infant formula manufacturer as necessary to control in order to prevent adulteration.

IFC Redlined Version

106.3(v) Critical is used to describe systems or equipment that have been designated by the infant formula manufacturer as necessary to control in order to prevent adulteration.

IFC Comment

This suggested definition of "critical" is introduced to provide a mechanism to reduce some of the unnecessary burden of this "validation" concept by limiting its scope to those areas of manufacture, which may truly have public health significance. It also emphasizes the responsibility of the manufacturer to make a careful determination of which areas may have this significance.

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FDA Proposed Regulation	IFC Suggested Language
Subpart B--Current Good Manufacturing Practice **106.5 Current good manufacturing practice.** 106.5(a) The regulations set forth in this subpart and, for liquid infant formulas, in part 113 of this chapter define the minimum current good manufacturing practices that are to be used in, and the facilities or controls that are to be used for, the manufacture, processing, packing, or holding of an infant formula. Compliance with these provisions is necessary to ensure that such infant formula provides the nutrients required under Sec. 107.100 of this chapter and is manufactured in a manner designed to prevent its adulteration. 106.5(b) The failure to comply with any regulation set forth in this subpart or, for liquid infant formulas, in part 113 of this chapter in the manufacture, processing, packing, or holding of an infant formula shall render such infant formula adulterated under section 412(a)(3) of the Federal Food, Drug, and Cosmetic Act (the act).	**Subpart B--Current Good Manufacturing Practice** **106.5 Current good manufacturing practice.** Acceptable as proposed. Acceptable as proposed, but note that "act" is already defined in proposed 106.1(a).
106.6 Production and in-process control system. 106.6(a) Manufacturers shall conform to the requirements of this subpart by implementing a system of production and in-process controls. This production and in-process control system shall cover all stages of processing, from the receipt and acceptance of the raw materials, ingredients, and components through the storage and distribution of the finished product and shall be designed to ensure that all the requirements of this subpart are met.	**106.6 Production and in-process control system.** 106.6(a) Manufacturers shall conform to the requirements of this subpart by implementing a system of production and in-process controls. This production and in-process control system shall cover those stages of processing, storage and distribution that are under the manufacturer's control, from the receipt and acceptance of the raw materials, ingredients, and components through the storage and distribution of the finished product, and shall be designed to ensure that all the requirements of this subpart are met.

IFC Redlined Version

106.6(a) Manufacturers shall conform to the requirements of this subpart by implementing a system of production and in-process controls. This production and in-process control system shall cover ~~all~~ those stages of processing, storage and distribution that are under the manufacturer's control, from the receipt and acceptance of the raw materials, ingredients, and components through the storage and distribution of the finished product, and shall be designed to ensure that all the requirements of this subpart are met.

IFC Comment

The requirement that the production and in-process control systems cover everything, including the distribution of finished product, could appear to extend beyond the time that the

manufacturer has control of the product. While a manufacturer should be required to maintain responsibility for its product through those distribution channels that are under its control, at the point that its control ends, the manufacturer cannot be expected to be responsible to assure proper distribution practices. That necessarily falls on another party. Also, when co packers are involved, the scope of responsibility of that party is necessarily limited to the specific aspect of manufacturing, storage or distribution that the co packer has been contracted to handle. The suggested wording change incorporates these concepts.

With respect to drugs, this concept is conveyed in 210.2(b).

FDA Proposed Regulation	IFC Suggested Language
106.6(b) The production and in-process control system shall be set out in a written plan, or set of procedures, that is designed to ensure that an infant formula is manufactured in a manner that will prevent adulteration of the infant formula.	Acceptable as proposed.
106.6(c) At any point, step, or stage in the production process where control is necessary to prevent adulteration, the manufacturer shall: 106.6(c)(1) Establish standards or specifications to be met;	106.6(c) The manufacturer shall identify the points, steps, or stages in the production process where control is critical to prevent adulteration. The manufacturer shall, with respect to such points: 106.6(c)(1) Establish specifications and, where appropriate, target values;

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106.6(c) ~~At any point, step, or stage~~ The manufacturer shall identify the points, steps, or stages in the production process where control is ~~necessary~~ critical to prevent adulteration~~,~~ ~~the~~. The manufacturer shall, with respect to such points:

106.6(c)(1) Establish ~~standards or~~ specifications and, where appropriate, target values ~~to be met~~;

IFC Comment

See the IFC's General Comment entitled Specifications and its proposed addition of the term definition above. As proposed, the language "any point, step, or stage..." refers, literally, to every conceivable manufacturing activity, for under the new legal standard that will begin with finalization of these regulations, there are few manufacturing activities that cannot, theoretically, give rise to a finding of "technical" adulteration. Obviously, it is impractical to fulfill the requirements of this proposed section for every conceivable manufacturing activity, so IFC's suggested revision focuses on the manufacturing steps most important to ensuring that a product is free from actual adulteration, and makes it consistent with proposed 106.100(e)(3). Finally, the IFC's suggested language also emphasizes that it is the responsibility of the manufacturer to identify the critical points.

FDA Proposed Regulation	IFC Suggested Language
106.6(c)(2) Monitor the production and in-process control point, step, or stage; 106.6(c)(3) Establish corrective action plans for use when a standard or specification established in accordance with paragraph (b)(1) of this section is not met;	Acceptable as proposed. 106.6(c)(3) Establish standard operating procedures to address when a specification established in accordance with paragraph (c)(1) of this section is not met;

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106.6(c)(3) Establish ~~corrective action plans for use when a standard or~~ standard operating procedures to address when a specification established in accordance with paragraph ~~(b)(1)~~ (c)(1) of this section is not met;

IFC Comment

The preamble to the proposed rule for this section states that "...the best way to ensure that a corrective action is appropriate is to determine the action in advance." While it may often be feasible to establish corrective action plans in advance, a manufacturer cannot be expected to foresee all future circumstances that may require reliance on a corrective action plans and to predict how it will operate. Certainly, the expectation and hope that an established corrective action plan can be applied to a problem is valid; however, many circumstances may have a different set of elements to be considered and they might require a case-by-case analysis. Consequently, the IFC's language requires a Standard Operating Procedure ("SOP") to be created to deal with results outside of specifications; there would be nothing to prevent a manufacturer from including typical potential corrective actions in that SOP, but those actions should not be mandated when they are irrelevant to the facts of a given situation.

Additionally, FDA's April announcement of the reopening of the comment period requested comments on the specific changes in current activities that would be required for companies to comply with the proposal. Corrective actions are based on scientific judgment and past experiences. If each specification needs to be tested to failure, the cost would be huge and would certainly prevent or severely limit new product development. Moreover, given the complex and multi-factorial aspects of infant formula production and the occasional failure of finished products to meet specifications, it is questionable whether such speculative actions would provide applicable guidance in a specific instance. If instead, scientific judgment supported by empirical evidence were allowed to determine which specifications should be challenged, some corrective action procedures might be identified in advance, but they would be limited to those situations that one would reasonably expect to encounter.

FDA Proposed Regulation	IFC Suggested Language
106.6(c)(4) Review the results of the monitoring required by paragraph (c)(2) of this section, and review and evaluate the public health significance of any deviations from standards or specifications that have been established in accordance with paragraph (c)(1) of this section. This review shall be conducted by an individual qualified by training and experience to conduct such reviews; and	106.6(c)(4) Review the results of the monitoring required by paragraph (c)(2) of this section, and review and evaluate whether deviations from specifications that have been established in accordance with paragraph (c)(1) of this section have public health significance. This review shall be conducted by an individual qualified by training and experience to conduct such reviews; and

IFC Redlined Version

106.6(c)(4) Review the results of the monitoring required by paragraph (c)(2) of this section, and review and evaluate ~~the public health significance of any~~ whether deviations from ~~standards or~~ specifications that have been established in accordance with paragraph (c)(1) of this section have public health significance. This review shall be conducted by an individual qualified by training and experience to conduct such reviews; and

IFC Comment

See the IFC's General Comment entitled Specifications. This proposed regulation incorporates the requirement to set specifications at the outer acceptability limits. The IFC is strongly opposed to this philosophy. Presently, IFC members utilize tight control limits, as distinguished from the broad outer limits that appear to be desired by FDA. If a tight limit is not met, a formal review is conducted and material disposition decisions are made based on that review. If the situation potentially involves a public health concern, the proper review by qualified individuals occurs. However, not all specifications involve concerns with public health significance. For example, shipper cartons that are found with a printing color that differs a shade or so from the tight color standard would not justify a public health significance evaluation.

IFC suggestions to address its opposition to the philosophy of the proposal on outer limit specifications include adding a definition for specification which permits manufacturers to establish specifications with tight limits, and that a result lying outside the tight specification does not trigger automatic rejection, but instead triggers a documented review. That is reflected above in the changes suggested by the IFC.

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FDA Proposed Regulation	IFC Suggested Language
106.6(c)(5) Establish Record keeping procedures, in accordance with Sec. 106.100(e)(3), that ensure that compliance with the requirements of this section is documented.	Acceptable as proposed.
106.10 Controls to prevent adulteration by workers. 106.10(a) There shall be sufficient personnel, qualified by training and experience, to perform all operations, including all required Record keeping, in the manufacture, processing, packing, and holding of each infant formula and to supervise such operations to ensure that they are correctly and fully performed.	**106.10 Controls to prevent adulteration by workers.** Delete or 106.10(a) The manufacturer shall designate sufficient personnel, qualified by training and experience, to perform all operations, including all required recordkeeping, in the manufacture, processing, packing, and holding of each infant formula and to supervise such operations to ensure that they are correctly and fully performed.

IFC Redlined Version

Delete
or
106.10(a) ~~There~~ The manufacturer shall ~~be~~ designate sufficient personnel, qualified by training and experience, to perform all operations, including all required recordkeeping, in the manufacture, processing, packing, and holding of each infant formula and to supervise such operations to ensure that they are correctly and fully performed.

IFC Comment

See the IFC's General Comment entitled Redundancy and Overly Prescriptive. The Food GMPs have numerous provisions relating to personnel. (See, e.g., section 110.10). The IFC questions whether the extensive, specific proposed provisions relating to personnel are all necessary.

The only standard by which one can demonstrate that "...sufficient personnel qualified by training and experience, to perform all operations..." have been employed by the manufacturer is by demonstrating that an unadulterated infant formula can be routinely manufactured. Other provisions of the existing and proposed regulations already require that unadulterated products be routinely manufactured. Thus, compliance with CGMP requirements should be adequate without the Agency's evaluation of internal staffing matters. Proposed section 106.10(a) is redundant with existing regulations and with other provisions of the proposed regulations and should be removed.

If FDA does not accept the IFC's suggested deletion and keeps this section in the final regulation, the preamble should acknowledge that "sufficiency" is determined by the manufacturer, based on its knowledge of its manufacturing and quality assurance systems. The suggested revision incorporates this concept. Moreover, current training programs have

been designed by the manufacturer to allow personnel to perform their required tasks. If FDA were to require different or more extensive training than deemed appropriate by the manufacturer, there would certainly be a large cost incurred by some manufacturers to implement and track those additional training programs.

FDA Proposed Regulation	IFC Suggested Language
106.10(b) Personnel working directly with infant formula, infant formula raw materials, infant formula packaging, or infant formula equipment or utensil contact surfaces shall practice good personal hygiene to protect the infant formula against contamination. Good personal hygiene includes, but is not limited to:	Delete.
106.10(b)(1) Wearing clean outer garments and, as necessary, protective apparel such as head, face, hands, and arm coverings; and 106.10(b)(2) Washing hands thoroughly in a hand washing facility with soap and running water at a suitable temperature before starting work, after each absence from the work station, and at any other time when the hands may become soiled or contaminated.	Delete. Delete.

IFC Redlined Version

~~106.10(b) Personnel working directly with infant formula, infant formula raw materials, infant formula packaging, or infant formula equipment or utensil contact surfaces shall practice good personal hygiene to protect the infant formula against contamination. Good personal hygiene includes, but is not limited to:~~

~~106.10(b)(1) Wearing clean outer garments and, as necessary, protective apparel such as head, face, hands, and arm coverings; and~~

~~106.10(b)(2) Washing hands thoroughly in a hand washing facility with soap and running water at a suitable temperature before starting work, after each absence from the work station, and at any other time when the hands may become soiled or contaminated.~~

IFC Comment

See the IFC's General Comment entitled Redundancy. Section 106.10(b) is redundant with the existing Food GMPs (§110.10(b)) and should, therefore, be removed from the final GMP document for infant formula.

FDA Proposed Regulation	IFC Suggested Language
106.10(c) Any person who reports that he or she has, or appears by medical examination or supervisory observation to have, an illness, open lesion, including boils, sores, or infected wounds, or any other source of microbial contamination that creates a reasonable possibility that the safety of an infant formula may be adversely affected, shall be excluded from direct contact with ingredients, containers, closures, in-process materials, equipment, utensils, and infant formula product until the condition is corrected or determined by competent medical personnel not to jeopardize the safety of the infant formula.	Delete.

IFC Redlined Version

~~106.10(c) Any person who reports that he or she has, or appears by medical examination or supervisory observation to have, an illness, open lesion, including boils, sores, or infected wounds, or any other source of microbial contamination that creates a reasonable possibility that the safety of an infant formula may be adversely affected, shall be excluded from direct contact with ingredients, containers, closures, in-process materials, equipment, utensils, and infant formula product until the condition is corrected or determined by competent medical personnel not to jeopardize the safety of the infant formula.~~

IFC Comment

See the IFC's General Comment entitled Redundancy. This language is virtually identical with provisions in the Food GMPs.

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FDA Proposed Regulation	IFC Suggested Language
106.20 Controls to prevent adulteration caused by facilities.	**106.20 Controls to prevent adulteration caused by facilities.**
106.20(a) Buildings used in the manufacture, processing, packing, or holding of infant formula shall be maintained in a clean and sanitary condition and shall have space for the separation of incompatible operations, such as the handling of raw materials, the manufacture of the product, and packaging and labeling operations.	Acceptable as proposed.
106.20(b) Separate areas shall be designated for holding raw materials, in-processing materials, and final product infant formula:	106.20(b) A control system shall be established by the manufacturer to control by status the storage and use of raw materials, in-process materials and finished infant formula. This system shall include the differentiation of the following:

IFC Redlined Version

106.20(b) ~~Separate areas shall be designated for holding~~ A control system shall be established by the manufacturer to control by status the storage and use of raw materials, in-processing materials, and ~~final product~~ finished infant formula. This system shall include the differentiation of the following:

IFC Comment

See the IFC's General Comment regarding Separate Storage Areas. The IFC believes that the Agency's proposal for physical separation of materials is extremely ill advised and perhaps impossible to implement. The physical separation of materials is neither practical nor necessary for the prevention of potential mix-ups during the manufacturing process. Therefore, it is recommended that this section be reworded as suggested to indicate that methods other than spatial separation are permissible for holding raw materials, in-process materials, and finished infant formula for the avoidance of potential mix-ups. Computerized inventory control or alternative methods currently used by IFC members, should be acknowledged as acceptable in the preamble to the final regulation, as should adequate marking of pallets. The requirement suggested by the IFC is comparable to that currently in effect for drugs pursuant to the GMP regulations for pharmaceuticals. The current process involves segregation of raw materials, released vs. non-released raw materials and in-process products and finished products, etc. by either a written card system or electronic tracking mechanism. If the process needs to be changed to have actual separation between raw materials, in processing materials and finished product; new facilities, utilities and infrastructure would need to be provided along with personnel to support these areas. The impact on resource requirements would be staggering, potentially hundreds of millions of dollars, with no value added to the product or benefits to the consumer.

FDA Proposed Regulation	IFC Suggested Language
106.20(b)(1) Pending release for use in infant formula production or pending release of the final product, 106.20(b)(2) After rejection for use in infant formula and before disposition, and	Acceptable as proposed. 106.20(b)(2) After rejection for use in or as infant formula, and

IFC Redlined Version

106.20(b)(2) After rejection for use in or as infant formula ~~and before disposition~~, and

IFC Comment

Once a decision is made concerning disposition, the requirement for proper status designation should not end, as it arguably does by the proposed language. Also, the addition of "or as" acknowledges the possibility that a finished batch may be rejected.

FDA Proposed Regulation	IFC Suggested Language
106.20(b)(3) After release for use in infant formula production or after release of the final product.	106.20(b)(3) After release for use in or as infant formula production or after release of the final product.

IFC Redlined Version

106.20(b)(3) After release for use in or as infant formula production or after release of the final product.

IFC Comment

See comment to 106.20(b)(2).

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FDA Proposed Regulation	IFC Suggested Language
106.20(c) Lighting shall allow easy identification of raw materials, packaging, labeling, in-process materials, and finished products that have been released for use in infant formula production and shall permit the easy reading of instruments and controls necessary in processing, packaging, and laboratory analysis. Any lighting fixtures directly over or adjacent to exposed raw materials, in-process materials, or bulk (unpackaged) finished product shall be protected to prevent glass from contaminating the product in the event of breakage.	Delete.

IFC Redlined Version

~~106.20(c) Lighting shall allow easy identification of raw materials, packaging, labeling, in-process materials, and finished products that have been released for use in infant formula production and shall permit the easy reading of instruments and controls necessary in processing, packaging, and laboratory analysis. Any lighting fixtures directly over or adjacent to exposed raw materials, in-process materials, or bulk (unpackaged) finished product shall be protected to prevent glass from contaminating the product in the event of breakage.~~

IFC Comment

See the General Comment regarding Redundancy. The Food GMPs (§110.35(b)(5)) fully describe the requirements for proper lighting in food plants.

FDA Proposed Regulation	IFC Suggested Language
106.20(d) Air filtration systems, including prefilters and particulate matter air filters, shall be used on air supplies to production areas where ingredients or infant formula are directly exposed to the atmosphere.	Delete.

IFC Redlined Version

~~106.20(d) Air filtration systems, including prefilters and particulate matter air filters, shall be used on air supplies to production areas where ingredients or infant formula are directly exposed to the atmosphere.~~

IFC Comment

See the IFC's General Comments entitled Overly Prescriptive and Redundancy. The Food GMPs (§110.35(b)(6)) establish requirements for ventilation. If FDA does not agree that the Food GMPs adequately address ventilation issues for infant formula manufacturers, it should consider utilizing language such as: "when there is reason to believe that the air in a particular area of the plant might result in adulteration of the product, measures should be

taken to prevent such adulteration, by air filtration or some other means."

In the April 2003 announcement of the reopening of the comment period, FDA specifically requested comment on the types and costs of air filtration systems used by infant formula manufacturers and the costs of making changes. U.S. Infant Formula Manufacturers currently use prefilters and in certain critical areas, particulate matter air filters, on their air supplies to production areas and in areas when the infant formula may be exposed to the atmosphere. Thus, this provision would not result in the expenditure of any additional funds. IFC believes a more detailed account of the types and costs of air filtration systems would be wasteful and would put an undue burden on industry, when there is no public interest served by insisting on specific changes in this arena.

FDA Proposed Regulation	IFC Suggested Language
106.20(e) All rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents shall be stored and used in a manner that protects against contamination of infant formula.	Delete.

IFC Redlined Version

~~106.20(e) All rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents shall be stored and used in a manner that protects against contamination of infant formula.~~

IFC Comment

See IFC's General Comment entitled "Redundancy." Section (e) is redundant with the Food GMPs (§110.35(b)(2)), and should, therefore, be removed.

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FDA Proposed Regulation	IFC Suggested Language
106.20(f)(1) Potable water used in the manufacture of infant formula shall meet the standards prescribed in the Environmental Protection Agency's (EPA's) Primary Drinking Water Regulations set forth in 40 CFR part 141, except that the fluoride level of the water used in infant formula manufacturing shall be as low as possible. The water shall be supplied under continuous positive pressure in a plumbing system that is free of defects that could contaminate an infant formula.	106.20(c)(1) Potable water used in infant formula shall meet the standards prescribed in the Environmental Protection Agency's (EPA's) Primary Drinking Water Regulations set forth in 40 CFR part 141, except that fluoride removal systems shall be employed for fluoridated water supplies. The water shall be supplied under continuous positive pressure in a plumbing system that is free of defects that could contaminate an infant formula.

IFC Redlined Version

106.20(~~f~~c)(1) Potable water used in ~~the manufacture of~~ infant formula shall meet the standards prescribed in the Environmental Protection Agency's (EPA's) Primary Drinking Water Regulations set forth in 40 CFR part 141, except that ~~the fluoride level of the water used in infant formula manufacturing shall be as low as possible~~ fluoride removal systems shall be employed for fluoridated water supplies. The water shall be supplied under continuous positive pressure in a plumbing system that is free of defects that could contaminate an infant formula.

IFC Comment

The requirement that fluoride levels for ingredient water be "as low as possible" is vague, potentially prohibitively costly, and unnecessary to prevent any public health concern. Although manufacturers strive to produce infant formula product with low fluoride levels, different technologies are utilized to achieve this goal. There is concern that Agency representatives could take the position that "as low as possible" means the most advanced, most expensive fluoride removal system available, which could cost millions of dollars to install, along with substantial increase in on-going operating costs all without any commensurate benefit to public health.

In order to reflect what we understand to be FDA's current position on the subject of fluoride, the preamble to the final regulation, like the preamble to the proposed regulation, should state that current practices in the industry are deemed acceptable.

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FDA Proposed Regulation	IFC Suggested Language
106.20(f)(2) Manufacturers shall test representative samples of the potable water drawn at a point in the system at which the water is in the same condition that it will be when it is used in infant formula manufacturing.	Acceptable; Renumbered as 106.20(c)(2).
106.20(f)(3) Manufacturers shall conduct the tests required by paragraph (f)(2) of this section with sufficient frequency to ensure that the water meets the EPA's Primary Drinking Water Regulations but shall not conduct these tests less frequently than annually for chemical contaminants, every 4 years for radiological contaminants, and weekly for bacteriological contaminants.	Acceptable; Renumbered as 106.20(c)(3).
106.20(f)(4) Manufacturers shall make and retain records, in accordance with §106.100(f)(1), of the frequency and results of testing of the water used in the production of infant formula.	Acceptable; Renumbered as 106.20(c)(4).
106.20(g) There shall be no backflow from, or cross-connection between, piping systems that discharge waste water or sewage and piping systems that carry water for infant formula manufacturing.	Delete.

IFC Redlined Version

106.20(~~f~~c)(2) Manufacturers shall test representative samples of the potable water drawn at a point in the system at which the water is in the same condition that it will be when it is used in infant formula manufacturing.

106.20(~~f~~c)(3) Manufacturers shall conduct the tests required by paragraph (f)(2) of this section with sufficient frequency to ensure that the water meets the EPA's Primary Drinking Water Regulations but shall not conduct these tests less frequently than annually for chemical contaminants, every 4 years for radiological contaminants, and weekly for bacteriological contaminants.

106.20(~~f~~c)(4) Manufacturers shall make and retain records, in accordance with §106.100(f)(1), of the frequency and results of testing of the water used in the production of infant formula.

~~106.20(g) There shall be no backflow from, or cross-connection between, piping systems that discharge waste water or sewage and piping systems that carry water for infant formula manufacturing.~~

IFC Comment

See IFC's General Comment entitled "Redundancy." Section (g) is redundant with the Food GMPs (§110.37(b)(5)), and should, therefore, be removed.

FDA Proposed Regulation	IFC Suggested Language
106.20(h) When steam comes in direct contact with infant formula, it shall be safe and free of rust and other particulate matter that may contaminate the formula. Boiler water additives in the steam shall be used in accordance with Sec. 173.310 of this chapter.	Delete.

IFC Redlined Version

~~106.20(h) When steam comes in direct contact with infant formula, it shall be safe and free of rust and other particulate matter that may contaminate the formula. Boiler water additives in the steam shall be used in accordance with 173.310 of this chapter.~~

IFC Comment

See the IFC General Comment entitled Redundancy. Section (h) deals with both adulterants and additives found in boiler water that may come in contact with the infant formula. The adulterants provisions are redundant with provisions of the existing Food GMPs. The provision concerning the use of food additives in boiler water is entirely redundant also with 21 CFR §173.310, in that the use of unapproved boiler water additives renders the food adulterated whether the proposed new section exists or not. For this reason, the proposed provision, section (h), duplicates existing regulations and serves no purpose. This section should be removed from the final regulation.

FDA Proposed Regulation	IFC Suggested Language
106.20(i) Each infant formula manufacturing site shall provide its employees with readily accessible toilet facilities and hand washing facilities that include hot and cold water, soap or detergent, and single-service towels and that are maintained in good repair and in a sanitary condition at all times, and that these facilities provide for proper disposal of the sewage. Doors to the toilet facility shall not open into areas where infant formula ingredients, containers, or closures are stored, or where infant formula is processed or stored.	Delete.

IFC Redlined Version

~~106.20(i) Each infant formula manufacturing site shall provide its employees with readily accessible toilet facilities and hand washing facilities that include hot and cold water, soap or detergent, and single-service towels and that are maintained in good repair and in a sanitary condition at all times, and that these facilities provide for proper disposal of the sewage. Doors to the toilet facility shall not open into areas where infant formula ingredients, containers, or closures are stored, or where infant formula is processed or stored.~~

IFC Comment

See the IFC's General Comment entitled Redundancy. Section (i) is redundant with the Food GMPs (110.37(d) and (e)), and should, therefore, be removed.

If FDA decides that it is not redundant and includes language in the final regulation, the requirement for single-service sanitary towels in toilet facilities should be modified to include air driers as an alternative. This alternative is available under both the food (110.37(e)(3)) and drug (211.52) GMP. The IFC also questions the value added by the proposal with respect to its application to finished inventory storage areas.

FDA Proposed Regulation	IFC Suggested Language
106.30 Controls to prevent adulteration caused by equipment or utensils.	**106.30 Controls to prevent adulteration caused by equipment or utensils.**
106.30(a) Equipment used in the manufacture, processing, packing or holding of an infant formula shall be of appropriate design and shall be installed to facilitate its intended function and its cleaning and maintenance.	Acceptable as proposed.
106.30(b) Equipment and utensils used in the manufacture, processing, packing, or holding of an infant formula shall be constructed so that surfaces that contact ingredients, in-process materials, or infant formula are made of nontoxic materials and are not reactive or absorptive. Such equipment and utensils shall be designed to be easily cleanable and to withstand the environment of their intended use. All surfaces that contact ingredients, in-process materials, or infant formula shall be cleaned, sanitized, and maintained to protect infant formula from being contaminated by any source. Sanitizing agents used on food-contact surfaces must comply with Sec. 178.1010 of this chapter.	Delete.

IFC Redlined Version

~~106.30(b) Equipment and utensils used in the manufacture, processing, packing, or holding of an infant formula shall be constructed so that surfaces that contact ingredients, in-process materials, or infant formula are made of nontoxic materials and are not reactive or absorptive. Such equipment and utensils shall be designed to be easily cleanable and to withstand the environment of their intended use. All surfaces that contact ingredients, in-process materials, or infant formula shall be cleaned, sanitized, and maintained to protect infant formula from being contaminated by any source. Sanitizing agents used on food-contact surfaces must comply with 178.1010 of this chapter.~~

IFC Comment

See the IFC's General Comment regarding Redundancy. Section (b) is redundant with the Food GMPs (§110.35(d)), and should, therefore, be removed.

If FDA opts to include this language despite the redundancy, one clarification is needed. There are particular areas, most notably in the infant formula powder manufacturing process, where frequent exposures to moisture must be avoided in order to prevent the possibility of microbiological contamination. There are, accordingly, some areas where wet cleaning is neither practical nor desirable. Although the paragraph could be interpreted to allow for these unique circumstances, a clarification statement would remedy this gray area. The Food GMP uses the terminology "as necessary" for special circumstances regarding cleaning and sanitizing. This addition would address this potential situation.

FDA Proposed Regulation	IFC Suggested Language
106.30(c) Manufacturers shall ensure that substances, such as lubricants or coolants, that are required for operation of infant formula manufacturing equipment, but that would render the infant formula adulterated if they contaminated the formula, do not come in contact with formula ingredients, containers, closures, or in-process materials or with infant formula itself.	106.30(b) Manufacturers shall ensure that substances, such as lubricants or coolants, that are required for operation of infant formula manufacturing equipment, but that would render the infant formula adulterated if they contaminated the formula, do not come in contact with formula ingredients, containers and closures (prior to the closing/sealing operation), or in-process materials or with infant formula itself in a manner not permitted by applicable food additive regulations.

IFC Redlined Version

106.30(eb) Manufacturers shall ensure that substances, such as lubricants or coolants, that are required for operation of infant formula manufacturing equipment, but that would render the infant formula adulterated if they contaminated the formula, do not come in contact with formula ingredients, containers~~,~~ and closures~~, or in~~ (prior to the closing/sealing operation), or in-process materials or with infant formula itself in a manner not permitted by applicable food additive regulations.

IFC Comment

This paragraph requires one clarification. The intent is to avoid the contact of substances such as lubricants and coolants with ingredients, containers, closures, in-process materials or the infant formula, which would result in adulteration through contamination. Although probably implied, the reference to containers and closures should mean prior to the closing/sealing operation where the hermetic seal is formed.

Finally, the last phrase has been suggested in order to make it consistent with applicable food additive regulations.

FDA Proposed Regulation	IFC Suggested Language
106.30(d)(1) Manufacturers shall ensure that instruments used for measuring, regulating, or controlling mixing time and speed, temperature, pressure, moisture, water activity, or other parameters at points where control is deemed necessary to prevent adulteration in the processing of an infant formula are accurate, easily read, properly maintained, and present in sufficient number for their intended use. The instruments and controls shall be tested for accuracy (calibrated) against a known reference standard before first use and thereafter at routine intervals, as specified in writing by the manufacturer of the instrument or control, or as otherwise deemed necessary to ensure the accuracy of the instrument. The known reference standard shall be certified for accuracy at routine intervals specified in writing by the manufacturer of the instrument, or as otherwise deemed necessary to ensure the accuracy of the instrument. Manufacturers shall make and retain records of the accuracy checks in accordance with Sec. 106.100(f)(2).	106.30(c)(1) Manufacturers shall ensure that instruments used for measuring, regulating, or controlling mixing time and speed, temperature, pressure, moisture, water activity, or other parameters at points where control is deemed critical by the infant formula manufacturer to prevent adulteration in the processing of an infant formula are accurate, easily read, properly maintained, and present in sufficient number for their intended use. The instruments and controls shall be tested for accuracy (calibrated) against a known reference standard on or before first use and thereafter at routine intervals, as specified in writing by the manufacturer of the instrument or control, or as otherwise deemed necessary by the infant formula manufacturer to ensure the accuracy of the instrument. The known reference standard shall be certified for accuracy at routine intervals specified in writing by the manufacturer of the instrument, or as otherwise deemed necessary by the infant formula manufacturer to ensure the accuracy of the instrument. Manufacturers shall make and retain records of the accuracy checks in accordance with Sec. 106.100(f)(2).

IFC Redlined Version

106.30(~~d~~c)(1) Manufacturers shall ensure that instruments used for measuring, regulating, or controlling mixing time and speed, temperature, pressure, moisture, water activity, or other parameters at points where control is deemed ~~necessary~~ critical by the infant formula manufacturer to prevent adulteration in the processing of an infant formula are accurate, easily read, properly maintained, and present in sufficient number for their intended use. The instruments and controls shall be tested for accuracy (calibrated) against a known reference standard on or before first use and thereafter at routine intervals, as specified in writing by the manufacturer of the instrument or control, or as otherwise deemed necessary by the infant formula manufacturer to ensure the accuracy of the instrument. The known reference standard shall be certified for accuracy at routine intervals specified in writing by the manufacturer of the instrument, or as otherwise deemed necessary by the infant formula manufacturer to ensure the accuracy of the instrument. Manufacturers shall make and retain records of the accuracy checks in accordance with Sec. 106.100(f)(2).

IFC Comment

There is no objection to the concept of calibration in this proposed section, but it could prove unduly burdensome if "drug" type compliance standards are applied to it. Including the qualification that the infant formula manufacturer bears the final responsibility for determining the frequency and scope of testing will help assure that the standard applied to infant formula is appropriate. Because of the broad scope and number of instruments to

which this rule will be applicable, it is possible that certain of these instruments may need to be in use while they are being calibrated. Therefore, it is suggested adding the words "on or" before first use to describe the timing of the initial certification.

In the Agency's April 2003 announcement of the reopening of the comment period, FDA requests comments on how often and under what conditions manufacturers now calibrate instruments and controls against a known standard and the adequacy of current procedures. U.S. Infant Formula Manufacturers have established calibration and preventative maintenance (PM) schedules for the appropriate pieces of equipment. As with the issue of validation, priorities for calibrations and PM are linked to criticality in regard to product quality and safety. Procedures and schedules are aligned according to the criticality assessments, which will vary from company to company, and are often based on the recommendations of the instrument supplier. Results of calibrations and PM's are trended. If trending data reflects a need to adjust the frequency, changes are made as required. For example, instruments used to monitor and release Infant Formula Products are calibrated at regular intervals. Most instruments are calibrated at three or six month intervals. A few instruments are calibrated at intervals longer or shorter based on experience while others are standardized at the time of use. Individual instrument performance is monitored and intervals adjusted based on historical performance. Process-monitoring equipment is typically calibrated at the location of the instrument installation. Traceable transfer standards are used to perform calibration at the location. Portable equipment (hand-held) is typically calibrated in an instrumentation lab in a standard environment.

Instruments are scheduled for calibration on a planned and periodic basis. Standards used to verify calibration are traceable to NIST or a recognized industry standard. Calibrations are performed per a written procedure with data recorded both before and after any adjustment if made. Whenever critical instruments are found significantly out-of-tolerance, they are reviewed and their impact on measurements is assessed. Assessment includes impact of any offset generally using data from back-up line instruments verifying performance to specification.

To conclude, the regulation should simply require that calibrations and preventive maintenance be performed on pre-established schedules and according to written procedures as determined by the infant formula manufacturer, based on information from the equipment supplier where applicable. If the new regulations require that all instruments need to be calibrated routinely, regardless of their function, this would require either the removal of all instruments not deemed critical by the infant formula manufacturer, or the addition of significant new personnel along with extensive systems to coordinate and track the calibration program.

FDA Proposed Regulation	IFC Suggested Language
106.30(d)(2) Instruments and controls that cannot be adjusted to agree with the reference standard shall be repaired or replaced.	Acceptable; Renumbered as 106.30(c)(2).
106.30(d)(3) If calibration of an instrument (testing for accuracy against a known reference standard) shows that a specification or standard for a point where control is deemed necessary to prevent adulteration has not been met, a written evaluation of all affected product, and of any actions that need to be taken with respect to that product, shall be made, in accordance with §106.100(f)(2).	Acceptable; Renumbered as 106.30(c)(3).
106.30(e)(1) The temperature in cold storage compartments that are used to store raw materials, in-process materials, or final product, and in thermal processing equipment used at points where temperature control is necessary to prevent adulteration, shall be monitored with such frequency as is necessary to ensure that temperature control is maintained.	Acceptable; Renumbered as 106.30(d)(1).
106.30(e)(2) Cold storage compartments shall be maintained at a temperature of 40 deg. F (4.4 deg. C) or below.	106.30(d)(2) Cold storage compartments shall be maintained at a temperature confirmed by the manufacturer to assure the quality and safety of raw or in-process materials.

IFC Redlined Version

106.30(~~d~~c)(2) Instruments and controls that cannot be adjusted to agree with the reference standard shall be repaired or replaced.

106.30(~~d~~c)(3) If calibration of an instrument (testing for accuracy against a known reference standard) shows that a specification or standard for a point where control is deemed necessary to prevent adulteration has not been met, a written evaluation of all affected product, and of any actions that need to be taken with respect to that product, shall be made, in accordance with §106.100(f)(2).

106.30(~~e~~d)(1) The temperature in cold storage compartments that are used to store raw materials, in-process materials, or final product, and in thermal processing equipment used at points where temperature control is necessary to prevent adulteration, shall be monitored with such frequency as is necessary to ensure that temperature control is maintained.

106.30(~~e~~d)(2) Cold storage compartments shall be maintained at a temperature ~~of 40 deg. F (4.4 deg. C), or below~~ confirmed by the manufacturer to assure the quality and safety of in-process materials.

IFC Comment

See the IFC Comment regarding Overly Prescriptive. Defining cold storage only as

40°F or lower is incompatible with the manufacture of quality infant formula. Such a prescriptive rule is arbitrary and potentially detrimental to the product. It is the practice of IFC members to cool in-process materials to temperatures that minimize the growth of microorganisms in the unsterile mix. In some situations, such as the long-term storage of aqueous solutions of nutrients that might support microbial growth, the use of 40°F as a storage temperature is well established to be appropriate and can thus be justified.

However, many materials stored at low temperatures in infant formula plants do not require the use of 40°F to ensure stability. In some cases, the use of temperatures this low may create quality problems involving mix destabilization and non-homogeneity, which could theoretically result in the final product being adulterated. (It should be noted that if it were necessary to insure that the temperature *never* rose above 40°F, the materials would actually have to be held at even lower temperatures most of the time, in order to allow a "margin".) The short period of time that some materials are held does not justify the use of a 40°F storage temperature. Thus, mandating an absolute maximum temperature *for all purposes* is not necessary to protect public health and would require additional capital investments for cooling capacity that would not add value to the product.

In summary, cold temperature storage conditions must be left up to the manufacturer to determine and be commensurate with batch sizes, hold times, and other important considerations that are not susceptible to prescription by regulatory requirements. The IFC believes that simply announcing the end point to be achieved, e.g., "cold storage will be maintained at temperatures that prevent growth of pathogenic microorganisms," is the preferable alternative.

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FDA Proposed Regulation	IFC Suggested Language
106.30(e)(3)(i) Cold storage compartments and thermal processing equipment shall be equipped with easily readable, accurate temperature-indicating devices.	Acceptable; Renumbered as 106.30(d)(3)(i).
106.30(e)(3)(ii) Thermal processing equipment shall be equipped with temperature-recording devices that will reflect the true temperature on a continuing basis. Cold storage compartments shall be equipped with either temperature-recording devices that will reflect the true temperature, on a continuing basis, within the compartment or, in lieu of a temperature-recording device, a high temperature alarm or a maximum-indicating thermometer that has been verified to function properly. If the manufacturer uses either of the latter options, it shall maintain a temperature log in which it notes temperature with such frequency as is necessary to achieve control. Manufacturers shall make and retain records, in accordance with Sec. 106.100(f)(3), of the temperatures indicated or recorded by these devices.	106.30(d)(3)(ii) Thermal processing equipment shall meet the requirements of 21 C.F.R. Part 113. Temperature monitoring of cold storage compartments shall be of sufficient frequency to assure proper control. Manufacturers shall make and retain records, in accordance with Sec. 106.100(f)(3), of the temperatures indicated or recorded by these devices.

IFC Redlined Version

106.30(~~e~~d)(3)(i) Cold storage compartments and thermal processing equipment shall be equipped with easily readable, accurate temperature-indicating devices.

106.30(~~e~~d)(3)(ii) Thermal processing equipment shall ~~be equipped with temperature-recording devices that will reflect the true temperature on a continuing basis. Cold~~ meet the requirements of 21 C.F.R. Part 113. Temperature monitoring of cold storage compartments shall be ~~equipped with either temperature-recording devices that will reflect the true temperature, on a continuing basis, within the compartment or, in lieu of a temperature-recording device, a high temperature alarm or a maximum-indicating thermometer that has been verified to function properly. If the manufacturer uses either of the latter options, it shall maintain a temperature log in which it notes temperature with such frequency as is necessary to achieve~~ of sufficient frequency to assure proper control. Manufacturers shall make and retain records, in accordance with Sec. 106.100(f)(3), of the temperatures indicated or recorded by these devices.

IFC Comment

See the IFC's Recurring Comments regarding Redundancy. Thermometer recording device requirements are governed by 21 CFR Part 113, with which this proposal is redundant. However, the requirement that the device will reflect the true temperature *conflicts* with 21 CFR Part 113, which requires a bias so that it reads no higher than the mercury-in-glass thermometer. This proposal also conflicts with 106.30(e)(4) which also indicates the need for bias. 21 CFR Part 113 more accurately reflects the needs of a thermal processing system, and the infant formula GMP should simply refer to this regulation.

Regarding the cold temperature storage temperature monitoring requirements, it is unnecessary to require recording devices or high temperature alarms. Temperature monitoring can be acceptably achieved through periodic manual recordings with sufficient frequency to assure proper temperature control. The large volume liquid mixes in the infant formula manufacturing process do not demonstrate significant temperature changes over time. IFC members typically are involved with volumes of 30,000 to 250,000 pounds of liquid mix. Shifts in temperature in these volumes are extremely slow and do not warrant the increased capital investment of recording devices and temperature alarms. Thus, it is easy to see why manual recordings at pre-determined intervals are more than adequate to monitor cold temperature storage conditions.

Finally, the preamble states that for calibration of thermometers for cold storage temperature measurements, "Manufacturers should do so at least at the beginning and end of each production day..." This frequency is totally unwarranted and would require significant extra resources to accomplish with absolutely no benefit. Again, the importance of these cold storage temperature measurements is grossly exaggerated in the proposal. The Agency is proposing a calibration frequency that is far more stringent than measurement devices for thermal food processing, which is a process of critical importance. The frequency for calibration of cold storage temperature measurement devices should be determined by the manufacturer based on the volume, hold time and location in the manufacturing process.

FDA Proposed Regulation	IFC Suggested Language
106.30(c)(4) When a temperature-recording device is used, such device shall not read higher than the calibrated temperature-indicating device for thermal processing equipment or lower than the reference temperature-indicating device for cold storage compartments.	Delete.

IFC Redlined Version

~~106.30(e)(4) When a temperature-recording device is used, such device shall not read higher than the calibrated temperature-indicating device for thermal processing equipment or lower than the reference temperature-indicating device for cold storage compartments.~~

IFC Comment

See the IFC General Comments regarding Redundancy. Again, the bias requirement for thermal process recording devices is redundant with 21 CFR Part 113. Simply referencing this regulation is sufficient, as is recommended in the IFC's comment to proposed 106.30(e)(ii). However, the proposal to bias cold storage temperature recorders is totally inappropriate. The proposal appears to equate the importance of a very slight temperature deviation for the sterilization process with a very slight temperature deviation for the cold storage compartment. The two situations are radically different. For example, a 1°F drop in the sterilization temperature would have a significant effect on the process lethality as

determined by the process authority and could result in the failure to meet commercial sterility; whereas a 1°F increase in the temperature of a cold storage compartment would have a very small impact on the growth of microorganisms. As mentioned in the IFC's comments to 106.30(e)(ii), there is no need for recording devices or high temperature alarms for cold storage compartments, and there certainly is no justification to require a bias in their recording measurements.

FDA Proposed Regulation	IFC Suggested Language
106.30(f) Equipment and utensils used in the manufacture of infant formula shall be cleaned, sanitized, and maintained at regular intervals to prevent adulteration of the infant formula. An individual qualified by training or experience to conduct such a review shall check all cleaning, sanitizing, and maintenance to ensure that it has been satisfactorily completed. Manufacturers shall make and retain records on equipment cleaning, sanitizing, and maintenance, in accordance with Sec. 106.100(f)(4).	106.30(e) Equipment and utensils used in an operating production line for the manufacture of infant formula shall be cleaned and sanitized at regular intervals as determined by the manufacturer to be necessary to prevent adulteration of the infant formula. An individual qualified by training or experience to conduct such a review shall check all cleaning and sanitizing, to ensure that it has been satisfactorily completed. Manufacturers shall make and retain records in accordance with Sec. 106.100(f)(4).

IFC Redlined Version

106.30(~~f~~e) Equipment and utensils used in an operating production line for the manufacture of infant formula shall be cleaned~~,~~ and sanitized~~, and maintained~~ at regular intervals as determined by the manufacturer to be necessary to prevent adulteration of the infant formula. An individual qualified by training or experience to conduct such a review shall check all cleaning~~,~~ and sanitizing, ~~and maintenance~~ to ensure that it has been satisfactorily completed. Manufacturers shall make and retain records ~~on equipment cleaning, sanitizing, and maintenance,~~ in accordance with Sec. 106.100(f)(4).

IFC Comment

See the IFC General Comment regarding Redundancy. Clarification is needed for the requirement regarding "regular intervals" of cleaning. If a certain production line, which requires daily cleaning and sanitizing, is taken out of service for some time, the "regular intervals" will no longer apply to this idle line. The Agency probably meant to couple "regular intervals" with lines that are operational.

The IFC is also confused by the inclusion of "maintained" and "maintenance" in this proposed section. If the intention of those words relates to major equipment repair, the IFC has no objection with their inclusion. If, however, it is intended to include every minor action that is taken to "maintain" equipment, then the proposal becomes extremely burdensome. It is potentially far too broad in the context of on-line equipment control. Coupled with this is the need to make and retain documentation, which would be extensive if every maintenance activity (e.g., changing an "O" ring) had to be documented. Because of the IFC's concern, it has suggested deleting the words "maintained" and "maintenance" in this section.

FDA Proposed Regulation	IFC Suggested Language
106.30(g) Compressed air or other gases that are mechanically introduced into infant formula, that are used to clean any equipment, or that come into contact with any other surface that contacts ingredients, in-process materials, or infant formula shall be treated in such a way that their use will not contaminate the infant formula with unlawful indirect food additives or other chemical, physical, or microbiological contaminants. When compressed gases are used at product filling machines to replace air removed from the headspace of containers, the manufacturer shall install a 0.5 micrometer or smaller filter as close to the end of the gas line that feeds gas into the space, as practical.	Delete.

IFC Redlined Version

~~106.30(g) Compressed air or other gases that are mechanically introduced into infant formula, that are used to clean any equipment, or that come into contact with any other surface that contacts ingredients, in-process materials, or infant formula shall be treated in such a way that their use will not contaminate the infant formula with unlawful indirect food additives or other chemical, physical, or microbiological contaminants. When compressed gases are used at product filling machines to replace air removed from the headspace of containers, the manufacturer shall install a 0.5 micrometer or smaller filter as close to the end of the gas line that feeds gas into the space, as practical.~~

IFC Comment

See the IFC General Comment regarding Redundancy. Under existing regulations, the introduction of unlawful indirect additives or adulterants into infant formulas, by way of gases or by any other means, is already unlawful. Therefore, section (g) should be removed, as it is redundant and serves no useful purpose.

FDA Proposed Regulation	IFC Suggested Language
106.35 Controls to prevent adulteration due to automatic (mechanical or electronic) equipment.	Delete.

IFC Redlined Version

~~106.35 Controls to prevent adulteration due to automatic (mechanical or electronic) equipment.~~

IFC Comment

See the IFC's General Comment regarding Validation, recommending that finalization

of section 106.35 be postponed until an appropriate task force can be convened to work out the details of its wording and implementation. If such a task-force approach is not acceptable to the Agency, then it is essential that the following issues be addressed in any final rule based on this proposal: (1) distinguishing food-compliance validation standards from drug-compliance standards; (2) limiting the scope of "validation" requirements to critical control points identified by the manufacturer; and (3) confirming the releasability of any product manufactured during "validation" processes if it complies with the requirements of the Infant Formula Act. Although the IFC continues to believe that postponement and a task-force approach would be the best way to achieve appropriate regulation in this area, we have listed the remaining subsections of section 106.35 below, along with our suggestions for addressing the issues identified above.

FDA Proposed Regulation	IFC Suggested Language
106.35(a)(1) For the purposes of this section, "hardware" means all automatic equipment, including mechanical and electronic equipment (including computers), that is used in production or quality control of a infant formula.	Delete, based on the IFC's Comment to proposed 106.35.
106.35(a)(2) For the purposes of this section, "software" means any programs, procedures, rules, and associated documentation used in the operation of a system.	Delete, based on the IFC's Comment to proposed 106.35.
106.35(a)(3) For the purposes of this section, "system" means a collection of components (including software and hardware) organized to accomplish a specific function or set of functions in a specified environment.	Delete, based on the IFC's Comment to proposed 106.35.
106.35(a)(4) For the purposes of this section, "validation" means establishing documented evidence that provides a high degree of assurance that a system will consistently produce a product meeting its predetermined specifications and quality characteristics.	Delete, based on the IFC's Comment to proposed 106.35.

IFC Redlined Version

~~106.35(a)(1) For the purposes of this section, "hardware" means all automatic equipment, including mechanical and electronic equipment (including computers), that is used in production or quality control of a infant formula.~~

~~106.35(a)(2) For the purposes of this section, "software" means any programs, procedures, rules, and associated documentation used in the operation of a system.~~

~~106.35(a)(3) For the purposes of this section, "system" means a collection of components (including software and hardware) organized to accomplish a specific function or set of functions in a specified environment.~~

~~106.35(a)(4) For the purposes of this section, "validation" means establishing documented~~

~~evidence that provides a high degree of assurance that a system will consistently produce a product meeting its predetermined specifications and quality characteristics.~~

IFC Comment

The IFC refers the Agency once again to the IFC's General Comment on Validation, where the Council has gone into detail about the problems inherent in applying this implied drug criterion to infant formula processing - problems which include an cost burden without attendant public health benefits, a disincentive to innovation and continuous process improvement, and the redundancy of mandating front-end validation to a process which is already required, by law, to be tested along so many critical parameters at the finished-product stage. While many aspects of the "validation" concept are already in use in infant formula manufacture, we highly recommend that a task force be utilized to determine how and to what extent appropriate aspects of the "validation" concept should be incorporated into infant formula GMPs.

If such an approach is not acceptable, however, the IFC suggests that at the very least, (a) FDA clarify what acceptable "validation" processes for infant formula would be in order to distinguish it from the "validation" used in drug manufacture, (b) FDA acknowledge that it is appropriate to leave to the manufacturer the identification of the critical control points to which validation should be applied; and (c) FDA confirm the releasability of any product manufactured during "validation" processes if it complies with the requirements of the Infant Formula Act.

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FDA Proposed Regulation	IFC Suggested Language
106.35(b)(1) All systems shall be designed, installed, tested, and maintained in a manner that will ensure that they are capable of performing their intended function and of producing or analyzing infant formula in accordance with this subpart and subpart C of this part.	Delete or 106.35(a)(1) All critical systems shall be designed, installed, tested, and maintained in a manner that will ensure that they are capable of performing their intended function and of producing or analyzing infant formula in accordance with this subpart and subpart C of this part.
106.35(b)(2) The infant formula manufacturer shall ensure that hardware is routinely calibrated, inspected, and checked according to written procedures.	Delete or 106.35(a)(2) The infant formula manufacturer shall ensure that critical hardware is routinely inspected and checked according to written procedures.

IFC Redlined Version

Delete
or
106.35(~~b~~a)(1) All critical systems shall be designed, installed, tested, and maintained in a manner that will ensure that they are capable of performing their intended function and of producing or analyzing infant formula in accordance with this subpart and subpart C of this part.

Delete
or
106.35(~~b~~a)(2) The infant formula manufacturer shall ensure that critical hardware is routinely ~~calibrated,~~ inspected~~,~~ and checked according to written procedures.

IFC Comment

See the IFC's suggested addition of the definition of "critical" in the definitions section of the regulation. (IFC suggested 106.3(v)). The IFC also suggests that "calibrated" be deleted, because it applies to instrumentation, not hardware.

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FDA Proposed Regulation	IFC Suggested Language
106.35(b)(3) The infant formula manufacturer shall check and document the accuracy of input into, and output generated by, any system used in the production or quality control of an infant formula. The degree and frequency of input/output verification shall be based on the complexity and reliability of the system and the level of risk associated with the safe operation of the system.	Delete or 106.35(a)(3) The infant formula manufacturer shall check and document the accuracy of input into, and output generated by, any critical system used in the production or quality control of an infant formula. The degree and frequency of input/output verification shall be based on the manufacturer's assessment of the complexity and reliability of the system and the level of risk associated with the safe operation of the system. Quality evaluations should be used to substantiate the adequacy of the checks required by this section.

IFC Redlined Version

Delete
or
106.35(~~b~~a)(3) The infant formula manufacturer shall check and document the accuracy of input into, and output generated by, any critical system used in the production or quality control of an infant formula. The degree and frequency of input/output verification shall be based on the manufacturer's assessment of the complexity and reliability of the system and the level of risk associated with the safe operation of the system. Quality evaluations should be used to substantiate the adequacy of the checks required by this section.

IFC Comment

The degree and frequency of input/output verification should be based on the manufacturer's assessment of the complexity and reliability of the system and the level of risk associated with the safe operation of the system. Nutrient test results should be used to substantiate the adequacy of the checks required by this section. The manufacturer should be responsible not only to determine which systems are critical to the prevention of adulteration but also to make appropriate assessments of the degree and frequency of verification necessary. The reference to nutrient testing reinforces the required testing and emphasizes the importance that testing plays in the assessment of new production systems. The accuracy of the input and output generated from an automated system is assessed by quality evaluations. If all automated systems need to be tested to prevent errors from faulty data entry, programming or equipment malfunction, new operator procedures and coding standards to include error trapping provisions will need to be developed at a cost that is not warranted and will not provide any additional security to the consumer.

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FDA Proposed Regulation	IFC Suggested Language
106.35(b)(4) The infant formula manufacturer shall ensure that all systems are validated before their first use to manufacture commercial product.	Delete or 106.35(a)(4) The infant formula manufacturer shall ensure that all critical systems are checked as per 106.35(b)(3) before the release of commercial product initially manufactured with these systems.

IFC Redlined Version

Delete
or
106.35(~~b~~a)(4) The infant formula manufacturer shall ensure that all critical systems are ~~validated before their first use to manufacture~~ checked as per 106.35(b)(3) before the release of commercial product initially manufactured with these systems.

IFC Comment

While most "validation" processes begin prior to the manufacturing of commercial product, the first commercial batch may be produced as part of the validation process. Assuming that such a batch meets all the requirements of the Infant Formula Act, there is no basis for rejecting it. If all systems need to be validated prior to the manufacture of any infant formula, this would result in a very large expense (up to hundreds of thousands of dollars) to destroy the product.

FDA Proposed Regulation	IFC Suggested Language
106.35(b)(5) The infant formula manufacturer shall ensure that any system that is modified is revalidated after the modification and before use of the modified system to manufacture commercial product. All modifications to software shall be made by a designated individual and shall be checked by the infant formula manufacturer to ensure that infant formula that is produced or analyzed using the modified software complies with this subpart and with subpart C of this part.	Delete or 106.35(a)(5) The infant formula manufacturer shall ensure that any critical system that is modified is reassessed after the modification and before release of any infant formula manufactured with the modified system. All modifications to critical software shall be made by a designated individual and shall be checked by the infant formula manufacturer to ensure that infant formula that is produced or analyzed using the modified software complies with this subpart and with subpart C of this part.

IFC Redlined Version

Delete
or
106.35(~~b~~a)(5) The infant formula manufacturer shall ensure that any critical system that is modified is ~~revalidated~~ reassessed after the modification and before ~~use of~~ release of any infant formula manufactured with the modified system ~~to manufacture commercial product~~. All modifications to critical software shall be made by a designated individual and shall be checked by the infant formula manufacturer to ensure that infant formula that is produced or analyzed using the modified software complies with this subpart and with subpart C of this

part.

IFC Comment

See the IFC's General Comment regarding Validation. Additionally, FDA's April announcement of the reopening of the comment period requested comments on the specific changes in current activities that would be required for companies to comply with proposal. Currently, only selected people can make revisions to software; however, additional documented training prior to allowing the person to have access may be required by this regulation.

FDA Proposed Regulation	IFC Suggested Language
106.35(c) The infant formula manufacturer shall make and retain records, in accordance with Sec. 106.100(f)(5), concerning automatic (mechanical or electronic) equipment.	Delete or 106.35(b) The infant formula manufacturer shall make and retain necessary records, in accordance with Sec. 106.100(f)(5), concerning critical automatic (mechanical or electronic) equipment.

IFC Redlined Version

Delete
or
106.35(eb) The infant formula manufacturer shall make and retain necessary records, in accordance with Sec. 106.100(f)(5), concerning critical automatic (mechanical or electronic) equipment.

IFC Comment

See the IFC's General Comment regarding Validation and Recordkeeping, as well as the IFC comment on the suggested definition of "critical" at 106.3(v).

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FDA Proposed Regulation	IFC Suggested Language
106.40 Controls to prevent adulteration caused by ingredients, containers, and closures.	**106.40 Controls to prevent adulteration caused by ingredients, containers, and closures.**
106.40(a) The only substances that may be used in infant formulas are food ingredients whose use in infant formula is safe and suitable under the applicable food safety provisions of the Federal Food, Drug, and Cosmetic Act; that is, the substance is generally recognized as safe (GRAS) for such use, is used in accordance with the agency's food additive regulations, or is authorized by a prior sanction.	Delete.
106.40(b) Infant formula containers and closures shall not be reactive or absorptive so as to affect the safety of the infant formula, and all packaging material that comes in contact with infant formula shall be composed of substances that are GRAS for use in or on food, GRAS for their intended use in food packaging, authorized by a prior sanction issued by the agency, or authorized for use as an indirect food additive. Any packaging material that comes in contact with infant formula shall be used in accordance with any prescribed limitations.	Delete.

IFC Redlined Version

~~106.40(a) The only substances that may be used in infant formulas are food ingredients whose use in infant formula is safe and suitable under the applicable food safety provisions of the Federal Food, Drug, and Cosmetic Act; that is, the substance is generally recognized as safe (GRAS) for such use, is used in accordance with the agency's food additive regulations, or is authorized by a prior sanction.~~

~~106.40(b) Infant formula containers and closures shall not be reactive or absorptive so as to affect the safety of the infant formula, and all packaging material that comes in contact with infant formula shall be composed of substances that are GRAS for use in or on food, GRAS for their intended use in food packaging, authorized by a prior sanction issued by the agency, or authorized for use as an indirect food additive. Any packaging material that comes in contact with infant formula shall be used in accordance with any prescribed limitations.~~

IFC Comment

See the IFC's General Comments regarding Redundancy. Under existing law and regulations, it is illegal to use an ingredient in an infant formula that is not GRAS, an approved food additive, or prior-sanctioned for such use. The same is true for packaging materials. Therefore, sections (a) and (b) are redundant and should be removed.

In addition, neither 106.40(a) nor 106.40(b) accurately reflects either current agency practice or the law. Proposed Section 106.40(a) actually can be read to be at odds with the GRAS notification process (in effect since 1997) which merely offers a "no objection" to GRAS status as opposed to a determination of GRAS status. Similarly, Section 106.40(b) does not reference the food contact substances Amendments of 1997. These omissions

simply underscore the wisdom and value of not proposing such a section: for not only does such a section bear the potential to be redundant but also runs the real risk of being antiquated by future policy and legislative developments.

FDA Proposed Regulation	IFC Suggested Language
106.40(c) Ingredients, containers, and closures used in the manufacture of infant formula shall be identified with a batch or lot number to be used in recording their disposition.	Acceptable; Renumbered as 106.40(a).
106.40(d) Infant formula manufacturers shall develop written specifications for their acceptance or rejection of ingredients, containers, and closures used in infant formula manufacture. These specifications shall stipulate the standards for acceptance or rejection of such ingredients, containers, and closures as well as the procedures for determining whether the ingredients, containers, and closures meet that standard. An individual qualified by training or experience shall conduct an investigation of a finding that any ingredients, containers, or closures used in a batch of infant formula failed to meet any of the manufacturer's specifications.	106.40(b) Infant formula manufacturers shall develop written specifications for ingredients, containers, and closures used as components in infant formula manufacture and packaging.

IFC Redlined Version

106.40(~~c~~a) Ingredients, containers, and closures used in the manufacture of infant formula shall be identified with a batch or lot number to be used in recording their disposition.

106.40(~~d~~b) Infant formula manufacturers shall develop written specifications for ~~their acceptance or rejection of~~ ingredients, containers, and closures used as components in infant formula manufacture~~. These specifications shall stipulate the standards for acceptance or rejection of such ingredients, containers, and closures as well as the procedures for determining whether the ingredients, containers, and closures meet that standard. An individual qualified by training or experience shall conduct an investigation of a finding that any ingredients, containers, or closures used in a batch of infant formula failed to meet any of the manufacturer's specifications~~ and packaging.

IFC Comment

See the IFC General Comment regarding Specifications. The IFC has suggested deleting a major portion of this proposal because it is covered in both 106.3(t), the suggested definition for "Specifications," and 106.6(c)(3) of the IFC suggestions and comments. Furthermore, the purpose and extent of the required investigation are unclear. Although, as modified, the language appears to be acceptable, several statements in the preamble are very troubling and deserve comment. First, the preamble suggests that indigenous nutrients should be included in raw material specifications and standards for acceptance or rejection. For certain ingredients, IFC members test for indigenous nutrient levels. However, the testing for indigenous nutrients in these cases is not for acceptance/rejection of the lot, but to determine the actual nutrient levels, which can be factored into specific batch formulations. For other ingredients, such as condensed skim milk, IFC members have an extensive history

in its use in infant formula and they can predict within a narrow range indigenous nutrient levels. Because of the experience with this ingredient, and the fact that the condensed skim milk provides 100% of several of the final product's nutrients, there is no need to assay the ingredient for specific batch formulations. Therefore, it is appropriate not to assay condensed skim milk for all indigenous nutrients. All nutrients required to be present in infant formula are tested and assured on each batch, as required by the Infant Formula Act, so any theoretical problems that might be presented would be detected through routine, legally mandated in-process and finished product testing. Requiring that raw materials be tested for all indigenous nutrients has significant impact on laboratory space, manpower, operating costs and potentially quality, all with no increased assurance of benefit to the final product or the consumer. As indicated in the actual language of the proposed rule, testing requirements for raw materials should be determined by the manufacturer.

Second, the preamble suggests that contaminants be included in the raw material specifications and standards for acceptance or rejection except as provided in compendial standards such as USP. This is inappropriate and unworkable. There are significant questions to be considered, such as how to decide which contaminants to test for in each ingredient, the determinations of acceptable/unacceptable levels, and detection vs. quantification scenarios. Even if one were to address these questions, the inclusion of routine contaminant testing in the infant formula industry would be grossly impractical due to the sophistication of the testing involved and the exorbitantly high costs associated with compliance. Again, testing requirements for raw materials should be determined by the manufacturer.

FDA Proposed Regulation	IFC Suggested Language
106.40(e) Ingredients, containers and closures shall be stored in areas clearly designated for:	106.40(c) Ingredients, containers and closures shall be controlled by a system that clearly designates:
106.40(e)(1) Materials pending release for use,	Acceptable; Renumbered as 106.40(c)(1).
106.40(e)(2) Materials released for use, or	Acceptable; Renumbered as 106.40(c)(2).

IFC Redlined Version

106.40(ec) Ingredients, containers and closures shall be ~~stored in areas~~ controlled by a system that clearly ~~designated for~~ designates:

106.40(ec)(1) Materials pending release for use,

106.40(ec)(2) Materials released for use, or

IFC Comment

See the IFC's General Comment regarding Separate Storage Areas and earlier comments to 106.20(b).

FDA Proposed Regulation	IFC Suggested Language
106.40(e)(3) Materials rejected for use in infant formula production. Any lot of ingredients, containers, or closures that does not meet the manufacturer's specifications shall be rejected and controlled under a quarantine system designed to prevent its use in the manufacture of infant formula.	106.40(c)(3) Materials rejected for use in infant formula production. Any lot of ingredients, containers, or closures that has been rejected shall be controlled under a quarantine system designed to prevent its use in the manufacture of infant formula, unless and until it is disposed of or reconditioned and found acceptable.

IFC Redlined Version

106.40(~~e~~c)(3) Materials rejected for use in infant formula production. Any lot of ingredients, containers, or closures that ~~does not meet the manufacturer's specifications shall be rejected and~~ has been rejected shall be controlled under a quarantine system designed to prevent its use in the manufacture of infant formula~~.~~, unless and until it is disposed of or reconditioned and found acceptable.

IFC Comment

See the IFC's General Comments regarding Specifications. The Agency's proposal includes the requirement that raw material specifications be set at the extreme acceptability limits. This poses the same problems as noted in the cited General Comment and the IFC's comments for 106.6(c)(1). The language suggested by the IFC removes references to specifications without removing the intention of the proposal to quarantine rejected materials until disposition activities are concluded.

FDA Proposed Regulation	IFC Suggested Language
106.40(f) If an ingredient, a container, or a closure that has been tested and examined is exposed to air, heat, or other conditions that may adversely affect it, the ingredient, container, or closure shall be retested or reexamined to ensure that it still meets the manufacturer's specifications.	106.40(d) If the manufacturer determines that an ingredient, a container, or a closure that has been tested and examined is exposed to conditions that could be expected to adversely affect it, the ingredient, container, or closure shall be retested or reexamined to ensure its acceptability for use in the manufacturing process.

IFC Redlined Version

106.40(~~f~~d) If the manufacturer determines that an ingredient, a container, or a closure that has been tested and examined is exposed to ~~air, heat, or other~~ conditions that ~~may~~ could be expected to adversely affect it, the ingredient, container, or closure shall be retested or reexamined to ensure ~~that it still meets the manufacturer's specifications.~~ its acceptability for use in the manufacturing process.

IFC Comment

The requirement to reexamine or retest any ingredient, container or closure, if it is found by the infant formula manufacturer to have been exposed to adverse storage conditions, is reasonable. However, this section can, logically, only apply when the manufacturer has knowledge of the potentially adverse conditions. To document control of

all storage areas, additional recording charts might be needed to provide continuous monitoring.

The preamble suggests that indigenous nutrients should be included in raw material specifications and standards for acceptance or rejection. For certain ingredients, indigenous nutrient levels are tested, however, the testing for indigenous nutrients in these cases is usually not for acceptance/rejection of the lot, but to determine the actual nutrient levels which can be factored into specific batch formulations. For other ingredients, such as condensed skim milk, IFC members have an extensive history in its use in infant formula and they can predict within a narrow range indigenous nutrient levels. All nutrients required to be present in infant formula are tested and assured on each batch, as required by the Infant Formula Act, so any theoretical problems that might be presented would be detected through routine, legally mandated in-process and finished product testing. Requiring that raw materials be tested for all indigenous nutrients would have a huge impact on laboratory space, manpower, operating costs and potentially quality, all with no increased assurance of benefit to the final product or the consumer.

The preamble also suggests that contaminants be included in the raw material specifications and standards for acceptance or rejection except as provided in compendia standards such as USP. There are significant questions to be considered, such as how to decide which contaminants to test for in each ingredient, the determinations of acceptable/unacceptable levels, and detection vs. quantification scenarios. The inclusion of routine contaminant testing in the infant formula industry would be impractical due to the sophistication of the testing involved and the very high costs associated with compliance. Contaminant testing is still undefined, so the program cost could vary significantly depending on the scope and volume of testing. If the testing included inorganic and organic compounds that would represent a broad range of contaminants (heavy metals, pesticides, herbicides, volatiles and semivolatiles), and the requirement is to test all ingredients being used in infant formula on an ongoing basis, cost would be astronomical. Moreover, the primary responsibility for meeting specifications regarding contaminants lies with the ingredient supplier, so as a matter of routine, a certificate of analysis or continuing guaranty from that supplier should be sufficient. Again, any testing requirements for raw materials should be determined by the infant formula manufacturer.

FDA Proposed Regulation	IFC Suggested Language
106.40(g) Manufacturers shall make and retain records, in accordance with §106.100(f)(6), on the ingredients, containers, and closures used in the manufacture of infant formula.	Acceptable; Renumbered as 106.40(e).

IFC Redlined Version

106.40(ge) Manufacturers shall make and retain records, in accordance with §106.100(f)(6), on the ingredients, containers, and closures used in the manufacture of infant formula.

FDA Proposed Regulation	IFC Suggested Language
106.50 Controls to prevent adulteration during manufacturing.	**106.50 Controls to prevent adulteration during manufacturing.**
106.50(a)(1) Manufacturers shall prepare and follow a written master manufacturing order that establishes controls and procedures for the production of an infant formula.	Acceptable as proposed.
106.50(a)(2) The manufacturer shall make and retain records, in accordance with §106.100(e), that include complete information relating to the production and control of the batch. An individual qualified by training or experience shall conduct an investigation of any deviations from the master manufacturing order and any corrective actions taken.	Acceptable as proposed.
106.50(a)(3) Changes made to the master manufacturing order shall be drafted, reviewed, and approved by a responsible official and include an evaluation of the effect of the change on the nutrient content and the suitability of the formula for infants.	Acceptable as proposed.
106.50(b) The manufacturer shall establish controls to ensure that each raw or in-process ingredient required by the master manufacturing order is examined by one person and checked by a second person or system. This checking will ensure that the correct ingredient is added during the manufacturing process, that the ingredient has been released for use in infant formula, and that the correct weight or measure of the ingredient is added to the batch.	Acceptable as proposed.

FDA Proposed Regulation	IFC Suggested Language
106.50(c) The manufacturer shall identify the contents, including the processing stage and the lot or batch number of a batch of infant formula, of all compounding and storage containers, processing lines, and major equipment used during the production of a batch of an infant formula.	106.50(c) The manufacturer shall establish a system that permits it to determine the major equipment systems used during the production of a batch of an infant formula.

IFC Redlined Version

106.50(c) The manufacturer shall ~~identify the contents, including the processing stage and the lot or batch number of a batch of infant formula, of all compounding and storage containers, processing lines, and major equipment~~ establish a system that permits it to determine the major equipment systems used during the production of a batch of an infant formula.

IFC Comment

The IFC is unclear what the Agency means by "identify" as that term relates to the

contents of equipment, processing lines and storage tanks. If the intent is physically to label these items, then the proposal is totally impractical because multitudes of equipment and lines are used in the production of infant formula, with several batches being processed and filled each day. Physical labeling would require a significant increase in manpower to apply and remove labels several times daily to accomplish this task with no benefit to the current operations. If "identify" means a system that permits determination of the location and movement of each batch, that would be a reasonable requirement.

If the operators need to document all the equipment that is being used additional personnel will be needed along with a system to track the equipment, and the resulting cost in manpower and interference with production timetables would be huge.

FDA Proposed Regulation	IFC Suggested Language
106.50(d) The manufacturer shall establish controls to ensure that the nutrient levels required by Sec. 107.100 of this chapter are maintained in the formula, and that the formula is not contaminated with microorganisms or other contaminants. Such controls shall include but not be limited to:	106.50(d) The manufacturer shall establish and document a system of controls to ensure that the nutrient levels required by Sec. 107.100 of this chapter are maintained in the formula, and that the formula is not contaminated with microorganisms or other contaminants.

IFC Redlined Version

106.50(d) The manufacturer shall establish and document a system of controls to ensure that the nutrient levels required by Sec. 107.100 of this chapter are maintained in the formula, and that the formula is not contaminated with microorganisms or other contaminants. ~~Such controls shall include but not be limited to:~~

IFC Comment

See the IFC's General Comment regarding Prescriptive Regulations. The intent of this paragraph is sound and is rightfully a part of the GMP regulations for infant formula. However, the Agency needs only to define the goal and general intent, as it has in this section, and not define exact parameters, as it has in the subparagraphs below 106.50(d), that could unintentionally prevent manufacturers from using other variations of production that could result in a perfectly acceptable product. For example, if a manufacturer could package an infant formula without the removal of air and still meet the nutritional and quality factors throughout shelf life, the flexibility for this approach should be allowed within this paragraph. The Agency should stop short of defining exacting in-process requirements, even as examples, and should let individual manufacturers determine the best and most economical approach to producing high quality infant formula that meets the end-points established by FDA. The manufacturer should then document its intended approach, as well as its compliance with its own designated control systems.

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FDA Proposed Regulation	IFC Suggested Language
106.50(d)(1) The mixing time; the speed, temperature, and flow rate of product; and other critical parameters necessary to ensure the addition of required ingredients to, and the homogeneity of, the formula;	Delete.
106.50(d)(2) The spray-drying process for powdered infant formula, including the filtering of the intake air before heating, to prevent microbial and other contamination;	Delete.
106.50(d)(3) The removal of air from the finished product to ensure that nutrient deterioration does not occur;	Delete.
106.50(d)(4) Ensuring that each container of finished product is properly sealed. Such controls shall involve use of established procedures, specifications, and intervals of examination that are designed by qualified individuals and are sufficient to:	Delete.
106.50(d)(4)(i) Detect visible closure or seal defects, and	Delete.
106.50(d)(4)(ii) Determine closure strength through destructive testing. Manufacturers of liquid infant formulas, which are thermally processed low-acid foods packaged in hermetically sealed containers, shall perform such closure integrity testing in accordance with Sec. 113.60(a) of this chapter.	Delete.

IFC Redlined Version

~~106.50(d)(1) The mixing time; the speed, temperature, and flow rate of product; and other critical parameters necessary to ensure the addition of required ingredients to, and the homogeneity of, the formula;~~

~~106.50(d)(2) The spray-drying process for powdered infant formula, including the filtering of the intake air before heating, to prevent microbial and other contamination;~~

~~106.50(d)(3) The removal of air from the finished product to ensure that nutrient deterioration does not occur;~~

~~106.50(d)(4) Ensuring that each container of finished product is properly sealed. Such controls shall involve use of established procedures, specifications, and intervals of examination that are designed by qualified individuals and are sufficient to:~~

~~106.50(d)(4)(i) Detect visible closure or seal defects, and~~

~~106.50(d)(4)(ii) Determine closure strength through destructive testing. Manufacturers of liquid infant formulas, which are thermally processed low-acid foods packaged in hermetically sealed containers, shall perform such closure integrity testing in accordance with 113.60(a) of this chapter.~~

IFC Comment

See the IFC's General Comments regarding Prescriptive Regulations, Redundancy, and the IFC's comments to 106.50(d). The requirements for closure evaluation are contained in 21 CFR 113 and do not need to be repeated in this paragraph.

FDA Proposed Regulation	IFC Suggested Language
106.50(e) The manufacturer shall establish controls that ensure that the equipment used at points where control is deemed necessary to prevent adulteration is monitored, so that personnel will be alerted to malfunctions.	Acceptable as proposed.
106.50(f) The manufacturer shall establish controls that ensure that rejected in-process materials:	Acceptable as proposed.
106.50(f)(1) Are clearly identified as having been rejected for use in an infant formula;	Acceptable as proposed.
106.50(f)(2) Are controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable;	Acceptable as proposed.
106.50(f)(3) Meet the appropriate specifications, if reprocessed, before being released for use in infant formula.	Delete or 106.50(f)(3) If subjected to reprocessing, meet the appropriate specifications or undergo a documented material disposition decision before being released for further use in infant formula.

IFC Redlined Version

Delete
or
106.50(f)(3) If subjected to reprocessing, ~~M~~meet the appropriate specifications~~, if reprocessed,~~ or undergo a documented material disposition decision before being released for further use in infant formula.

IFC Comment

If the IFC's suggested definition of specifications is accepted, the IFC suggests deleting this language, because its definition would address the situation described in this proposed paragraph. See the IFC's General Comment regarding Specifications.

The proposed wording is also awkward. It might mean that in-process materials for reprocessing or rework must meet specifications prior to use in infant formula. This would defeat the purpose for rework and reprocessing, because the purpose of these measures is to correct in-process deviations and achieve an acceptable finished product. If this interpretation were correct, this paragraph would have a significant financial impact on the manufacturer by requiring that all out of specification in-process material be rejected.

<table>
<tr><th>FDA Proposed Regulation</th><th>IFC Suggested Language</th></tr>
<tr><td>106.55 Controls to prevent adulteration from microorganisms.</td><td>106.55 Controls to prevent adulteration from microorganisms.</td></tr>
<tr><td>106.55(a) Manufacturers of liquid infant formula shall comply with the procedures specified in part 113 of this chapter for liquid infant formula.</td><td>Acceptable as proposed.</td></tr>
<tr><td>106.55(b) Manufacturers of powdered infant formula shall test representative samples of every batch of the formula at the final product stage, before distribution, to ensure that the infant formula meets the microbiological quality standards listed in paragraph (c) of this section.</td><td>Acceptable as proposed.</td></tr>
<tr><td>106.55(c) Any powdered infant formula that contains any microorganism that exceeds the M value listed for that microorganism in Table 1 of this section will be deemed to be adulterated under sections 402 and 412 of the Federal Food, Drug, and Cosmetic Act (the act). FDA will determine compliance with the M values listed below using the Bacteriological Analytical Manual (BAM), 8th ed. (1995), published by the AOAC International Association of Official Analytical Chemists, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR part 51. Copies are available from the Association of Official Analytical Chemists, 481 North Frederick Ave., Suite 500, Gaithersburg, MD 20877, or may be examined at the Center for Food Safety and Applied Nutrition's Library, 200 C St. SW, rm. 3321, Washington, DC, or may be examined at the Office of the Federal Register, 800 North Capitol St. NW, Suite 700, Washington, DC.</td><td>Acceptable as proposed, with the exceptions in the table below:</td></tr>
<tr><td><table>
<tr><th>Microorganism</th><th>M Value</th></tr>
<tr><td>Aerobic Plate Count (APC)</td><td>10,000 CFU/gram (g).[2]</td></tr>
<tr><td>Coliforms[3]</td><td>3.05 MPN/g.[4,5]</td></tr>
<tr><td>Fecal coliforms[6]</td><td>3.05 MPN/g.</td></tr>
<tr><td>Salmonella</td><td>0.[7]</td></tr>
<tr><td>Listeria monocytogenes</td><td>0.[7]</td></tr>
<tr><td>Staphylococcus aureus</td><td>3.05 MPN/g.</td></tr>
<tr><td>Bacillus cereus[8]</td><td>100 MPN/g or CFU/g.</td></tr>
</table></td><td><table>
<tr><th>Microorganism</th><th>M Value[1]</th></tr>
<tr><td>Aerobic Plate Count (APC)</td><td>10,000 CFU/gram (g).[2]</td></tr>
<tr><td>Enterobacteriaceae (EB)[3]</td><td>3.0 MPN/g.[4,5]</td></tr>
<tr><td>Fecal coliforms[6]</td><td>0.[7]</td></tr>
<tr><td>Salmonella</td><td>0.[7]</td></tr>
<tr><td>Staphylococcus aureus</td><td>3.0 MPN/g.</td></tr>
<tr><td>Bacillus cereus[8]</td><td>1000 CFU/g.</td></tr>
</table></td></tr>
<tr><td>[1] The M value is the maximum allowable number of microorganisms present in 1 g of dry infant formula.
[2] CFU/g, colony forming units per g.

[3] M values for coliforms greater than 3.05 are not violative if testing for fecal coliforms results in an M value equal to or less than 3.05.
[4] MPN/g, most probable number per g.
[5] The MPN value of 3.05 in this table is derived from the tables of calculated MPN values that appear in the 8th ed. of the BAM when using an inoculation series of 0.1, 0.01, and 0.001g (or ml) of the infant formula sample.

[6] No testing for fecal coliforms is required when the M value for coliforms is less than or equal to 3.05.
[7] None detected.
[8] B. cereus testing must be performed only if the APC exceeds 100 CFU/g.</td><td>[1] The M value is the maximum allowable number of microorganisms present in 1 g of dry infant formula.
[2] CFU/g, colony forming units per g. Probiotic infant formulas are exempted.
[3] M values for EB greater than or equal to 3.0 are not violative if fecal coliforms are not confirmed in the EB test.

[4] MPN/g, most probable number per g.
[5] The MPN value of 3.0 in this table is derived from the tables of calculated MPN values that appear in the January 2001 revision of the 8th ed. of the BAM when using an inoculation series of 0.1, 0.01, and 0.001g (or ml) of the infant formula sample.
[6] No confirmation testing for fecal coliforms is required when the M value for EB is less than 3.0.
[7] None detected.
[8] B. cereus testing must be performed only if the APC exceeds 1000 CFU/g (except for probiotic infant formulas)</td></tr>
</table>

IFC Redlined Version (partial for space saving)

Microorganism	M Value[1]
Aerobic Plate Count (APC)	10,000 CFU/gram (g).[2]
Enterobacteriaceae (EB)[3]	3.0~~5~~ MPN/g.[4,5]
Fecal coliforms[6]	~~3.05 MPN/g.~~ 0.[7]
Salmonella	0.[7]
~~*Listeria monocytogenes*~~	~~0.~~[7]
Staphylococcus aureus	3.0~~5~~ MPN/g.
Bacillus cereus[8]	~~100~~ 1000 CFU/g.

[1] The M value is the maximum allowable number of microorganisms present in 1 g of dry infant formula.
[2] CFU/g, colony forming units per g. Probiotic infant formulas are exempted.
[3] M values for EB ~~coliforms~~ greater than or equal to 3.0~~5~~ are not violative if ~~testing for~~ fecal coliforms are not confirmed in the EB test ~~results in an M value equal to or less than 3.05~~.
[4] MPN/g, most probable number per g.
[5] The MPN value of 3.0~~5~~ in this table is derived from the tables of calculated MPN values that appear in the January 2001 revision of the 8th ed. of the BAM when using an inoculation series of 0.1, 0.01, and 0.001g (or ml) of the infant formula sample.
[6] No confirmation testing for fecal coliforms is required when the M value for EB ~~coliforms~~ is less than ~~or equal to~~ 3.0~~5~~.
[7] None detected.
[8] *B. cereus* testing must be performed only if the APC exceeds 1000 ~~100~~ CFU/g (except for probiotic infant formulas).

IFC Comment

The IFC questions the need to conduct Listeria testing. Historical screening for Listeria in infant formula products has never revealed the presence of this organism. In addition, infant formula ingredients and products undergo several heat treatments. The supplier has already pasteurized the incoming milk; the in-process infant formula mix is pasteurized at least once again before drying. These multiple heat treatments are very effective for microbiological control of infant formula.

For the testing of *B. cereus*, the proposed specification to 100 CFU/g maximum allowance is lower than the earlier proposed maximum of 1000 CFU/g. Neither the IFC's literature review nor industry field experience indicates a health concern associated with *B. cereus* levels of 1000 CFU/g, let alone 100 CFU/g. The infectious dose of *B. cereus* for infants is unknown. The proposed CFR wording is based upon a concern for product abuse, i.e., storage of rehydrated product for 24 hours at 26°C (79°F). Label instructions clearly indicate the need to store rehydrated product under refrigeration and to discard formula immediately after feeding.

Because of the Agency's concerns with the emerging, opportunistic pathogen, *E. sakazakii* – arising from an outbreak of disease in premature infants – FDA's April 2003 announcement of the reopening of the comment period on this proposal requested comments on whether there is a need to include a microbiological requirement for *E. sakazakii* and, if so, what requirement the Agency should consider to ensure the safety of powdered infant formula and prevent future outbreaks. The Agency also requested comment on what other

changes, if any, in the proposed microbiological requirements would be appropriate to ensure the safety of powdered infant formula and to prevent outbreaks of illness. Given the excellent safety record of infant formula since the passage of the act, IFC does not see a real need for additional microbiological requirements to be added here. In particular, IFC questions the practicality of including specific microbiological specifications in the GMP regulations given the length of time required to pass or change such regulations. Perhaps, when the Agency encounters emerging pathogens of concern in the future, it could use a mechanism for establishing interim requirements that is less burdensome than the GMP regulations. A guidance document, based soundly on scientific and industrial input to ensure both reliability and feasibility would be easier to create and manage.

Relevant to a manufacturer's intended use of *Bifidobacterium lactis* strain Bb12 and *Streptococcus thermophilus* strain Th4 as ingredients in infant formula, the Agency's April announcement requested comment on what changes, if any, in the proposed microbiological requirements would be appropriate to provide for powdered infant formula and to ensure its safety if microorganisms are intentionally added to infant formulas. It's not clear that the proposed microbiological requirements would have any negative impact at all on the addition of beneficial organisms to infant formula. Currently, infant formula products marketed worldwide may contain anaerobic and/or facultative anaerobic microorganisms that have been intentionally included ("probiotics"). While it is possible that some infant formulas supplemented with approved probiotics might exceed the aerobic plate count, others would not. Those beneficial bacteria that are anaerobic would not even contribute to the number of microorganisms in the aerobic plate count (APC) as they would not be supported with the proper environmental conditions for growth.

Nevertheless, products with intentionally added microorganisms should be exempt from the proposed product aerobic plate count limit. It is appropriate for the APC limit to be excluded for this type of product, as long as it is replaced by more reliance on sanitation-indicative testing. For example, direct limits for Enterobacteriaceae, would be placed on these products. Additional testing that is typically required only when APC limitations are exceeded (e.g., *B. cereus*) would be automatically required for such products. This would be similar to the currently recommended evaluation of cultured dairy products (e.g., cottage cheese, yogurt, and sour cream).

Given that sampling and testing for microbiological endpoints continue to be areas where there is variability, and thus uncertainty of results, IFC urges FDA to move forward, in conjunction with the infant formula industry, toward defining sampling and testing methods in association with establishing microbiological specifications. Setting up two-class or three-class plans, as proposed by ICMSF and recognized by Codex, would be one avenue to pursue toward this aim.

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FDA Proposed Regulation	IFC Suggested Language
106.55(d) Manufacturers shall make and retain records, in accordance with §106.100(e)(5)(ii) and (f)(7), on the testing of infant formulas for microorganisms.	Acceptable as proposed.
106.60 Controls to prevent adulteration during packaging and labeling of infant formula.	**106.60 Controls to prevent adulteration during packaging and labeling of infant formula.**
106.60(a) Manufacturers shall examine packaged and labeled infant formula during finishing operations to ensure that containers and packages in the lot have the correct label, the correct use-by date, and the correct code established under §106.80.	Acceptable as proposed.
106.60(b) Labels shall be designed, printed, and applied so that the labels remain legible and attached during the conditions of processing, storage, handling, distribution, and use.	106.60(b) Labels shall be designed, printed, and applied so that the labels remain legible and attached during the conditions of processing, storage, handling, and distribution.

IFC Redlined Version

106.60(b) Labels shall be designed, printed, and applied so that the labels remain legible and attached during the conditions of processing, storage, handling, and distribution~~, and use~~.

IFC Comment

Labels often have coupons or second-language directions printed on the inside (i.e., they are "designed" and "printed" to come off), and the words "and use" in the proposal would negate this consumer benefit.

FDA Proposed Regulation	IFC Suggested Language
106.60(c) All infant formulas held in a single package shall be the same product bearing the same code, established under Sec. 106.80. Packaging used to hold multiple containers of infant formula shall be labeled with the product name, the name of the manufacturer or shipper, and the code.	106.60(c) Packaging used to hold multiple containers of the same type of infant formula shall be labeled with the product name, the name of the manufacturer, distributor or shipper, and the lot number. Packaging used to hold containers of different types of infant formula shall be labeled with the product names, the name of the manufacturer, responsible party or shipper, a lot number code that can serve to identify the contents, and an expiration date reflecting a shelf life no greater than the container exhibiting the shortest expiration date.

IFC Redlined Version

106.60(c) ~~All infant formulas held in a single package shall be the same product bearing the same code, established under Sec. 106.80.~~ Packaging used to hold multiple containers of the same type of infant formula shall be labeled with the product name, the name of the manufacturer, distributor or shipper, and the lot number. Packaging used to hold containers of different types of infant formula shall be labeled with the product names, the name of the manufacturer, responsible party or shipper, a lot number code that can serve to identify the contents, and an expiration date reflecting a shelf life no greater than the container exhibiting

the shortest expiration date.

IFC Comment

For the majority of cases, an infant formula package holding multiple containers will be all of the same product bearing the same code. However, there needs to be an allowance for "kits," which are commonly used in the industry to familiarize new mothers with infant formula prior to discharge from the hospital. These kits are designed to hold samples of different products. Therefore, they necessarily contain products with different codes and are so labeled. These kits are assigned a unique lot number for traceability purposes. The IFC believes that the intention of the Agency is not to eliminate "kits," which would disserve consumers and hospitals and which would have a substantial impact on the respective marketing programs of each company. Therefore, the IFC requests that the regulations be written to allow "kits."

FDA Proposed Regulation	IFC Suggested Language
106.70 Controls on the release of finished infant formula. 106.70(a) The manufacturer shall hold, or maintain under its control, each batch of infant formula until it determines that the batch meets all of its specifications, including those adopted to meet the requirements of Sec. 106.55 on microbiological contamination and Sec. 106.91(a) on quality control procedures, and releases the batch for distribution.	**106.70 Controls on the release of finished infant formula.** 106.70(a) The manufacturer or responsible party shall hold, or maintain under its control, each batch of infant formula until it determines that the batch meets the requirements of 21 CFR Part 106.

IFC Redlined Version

106.70(a) The manufacturer or responsible party shall hold, or maintain under its control, each batch of infant formula until it determines that the batch meets ~~all of its specifications, including those adopted to meet~~ the requirements of ~~106.55 on microbiological contamination and 106.91(a) on quality control procedures, and releases the batch for distribution.~~ 21 CFR Part 106.

IFC Comment

See the IFC's General Comment regarding Specifications. As that General Comment and the comments to 106.6(c)(1) state, the IFC believes that manufacturers should be encouraged to set tight specifications, and that the failure to meet such tight specifications should not automatically result in rejected product. As mentioned previously, product failing to meet the tighter specifications would be properly reviewed for disposition purposes. Of course, the manufacturer must meet all specifications listed in 106.55 and the requirements in 106.91(a), which are included in the requirements of Part 106.

FDA Proposed Regulation	IFC Suggested Language
106.70(b) Each batch of infant formula that fails to meet the manufacturer's specifications shall be rejected. Although the batch may be reprocessed, any batch of infant formula that is reprocessed shall be shown to meet the requirements of Sec. 106.70(a) before it is released.	106.70(b) Each batch of infant formula that fails to meet the requirements of Sec. 106.70(a) shall be rejected. Although the batch may be reprocessed, any batch of infant formula that is reprocessed shall be shown to meet the requirements of Sec. 106.70(a) before it is released.

IFC Redlined Version

106.70(b) Each batch of infant formula that fails to meet the ~~manufacturer's specifications~~ requirements of Sec. 106.70(a) shall be rejected. Although the batch may be reprocessed, any batch of infant formula that is reprocessed shall be shown to meet the requirements of Sec. 106.70(a) before it is released.

IFC Comment

See General Comments regarding Specifications. As noted in 106.6(c)(1) and 106.50(f)(3), the IFC neither wishes to widen specifications to the outer acceptability limits nor eliminate the purpose for rework and reprocessing.

FDA Proposed Regulation	IFC Suggested Language
106.70(c) An individual qualified by training or experience shall conduct an investigation of a finding that a batch of infant formula fails to meet any manufacturer's specifications.	106.70(c) An individual qualified by training or experience shall conduct an investigation of a finding that a batch of infant formula fails to meet any manufacturer's or responsible party's specifications in order to ensure that such failure does not lead to the release of adulterated product.

IFC Redlined Version

106.70(c) An individual qualified by training or experience shall conduct an investigation of a finding that a batch of infant formula fails to meet any manufacturer's ~~specifications.~~ or responsible party's specifications in order to ensure that such failure does not lead to the release of adulterated product.

IFC Comment

See the IFC General Comment regarding Definition of Manufacturer. The IFC has also suggested language from section 106.40 indicating the purpose and extent of the required investigation.

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FDA Proposed Regulation	IFC Suggested Language
106.80 Traceability.	**106.80 Traceability.**
106.80(a) Manufacturers shall ensure traceability by coding infant formulas in conformity with the coding requirements prescribed in §113.60(c) of this chapter for thermally processed low-acid foods packaged in hermetically-sealed containers, except as provided in paragraph (b) of this section.	Acceptable as proposed.
106.80(b) Batches of powdered infant formula that are manufactured in stages over more than 1 day, in lieu of being coded in accordance with §113.60(c) of this chapter, may be coded with a sequential number that identifies the product and the establishment where the product was packed and that permits tracing of all stages of manufacture of that batch, including the year, the days of the year, and the period during those days that the product was packed, and the receipt and handling of raw materials used.	Acceptable as proposed.
106.90 Audits of current good manufacturing practice.	**106.90 Audits of current good manufacturing practice.**
Manufacturers of an infant formula, or an agent of such manufacturers, shall conduct regularly scheduled audits to determine whether the manufacturer has complied with the current good manufacturing practice regulations in this subpart. These audits shall be performed by an individual who, as a result of education, training, and experience, is knowledgeable in all aspects of infant formula production and of the agency's regulations concerning current good manufacturing practice but who has no direct responsibility for the matters being audited.	Manufacturers of an infant formula, or an agent of such manufacturers, shall conduct regularly scheduled audits to determine whether the manufacturer has complied with the current good manufacturing practice regulations in this subpart. These audits shall be performed by an individual who, as a result of education, training, and experience, is knowledgeable of infant formula production and of the agency's regulations concerning good manufacturing practices but who has no direct responsibility for the matters being audited.

IFC Redlined Version

106.90 --Audits of current good manufacturing practice.

Manufacturers of an infant formula, or an agent of such manufacturers, shall conduct regularly scheduled audits to determine whether the manufacturer has complied with the current good manufacturing practice regulations in this subpart. These audits shall be performed by an individual who, as a result of education, training, and experience, is knowledgeable ~~in all aspects~~ of infant formula production and of the agency's regulations concerning good manufacturing practices but who has no direct responsibility for the matters being audited.

IFC Comment

The Agency proposes that an auditor be knowledgeable in "all" aspects of infant formula production. This is a very lofty expectation given the complexities of an infant formula production environment which entails raw materials, blending/mixing, processing, standardization, filling, sterilization/drying, packing, warehousing, shipping, maintenance,

cleaning, lab testing, documentation control, batch record review/release, training, etc. The phrase seems to imply that the auditor must be a supreme expert within the plant who knows all there is to know about infant formula production.

The IFC believes it is sufficient for an auditor to possess a general knowledge of these areas, but certainly he or she need not have knowledge to the depth and extent as the use of the word "all" in the proposal may imply. Such knowledge would entail years of cross training and constant retraining. The IFC believes that removing the word "all" does not diminish the intent of the Agency in this proposal.

The IFC agrees with the Agency's statement that the auditor shall have "no direct responsibility for the matters being audited." However, the preamble suggests that the auditor shall have no "past involvement in the activities being audited." This is a potential "Catch 22," and troublesome in that the proposed regulations seem to want the auditor to have knowledge of infant formula production, but have no past involvement where knowledge might have been gained. It's understandable that the regulations do not want the auditor to evaluate areas in which he or she had responsibility. It's equally understandable that an auditor should not evaluate an area in which he or she has recently worked, due to potential biases created by the previous position. However, a reasonable time should be established after which any concern about potential bias would dissipate and an auditor could evaluate an area of previous employment. If the Agency feels the need to specify a time limit in the regulation, the IFC suggests that limit be one year. Thus, an auditor would be allowed to audit an area of previous employment one year after departure.

Finally, the preamble also suggests that "regularly scheduled audits of all deviations" should be incorporated. As stated earlier in 106.6(c)(1), IFC members want the final regulations to allow specifications much tighter than the outer acceptability limits proposed by the Agency. See the IFC's General Comment regarding Specifications. This will obviously result in significantly more out-of-specification situations (which will each require a review for disposition) than will result if the outer acceptability limits proposed by FDA are required. It should be appreciated that the increased numbers of deviations under the IFC's proposal does not signify a process out of control, but instead the inevitable result of a manufacturer's desire to keep the process centered as tightly as possible. If the IFC's tighter specification allowance is incorporated in the final regulation, it does not feel that the auditor should be required to review "all" deviations. In such a case, the IFC would suggest requiring that a random sampling of deviations be reviewed.

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FDA Proposed Regulation	IFC Suggested Language
Subpart C--Quality Control Procedures **106.91 General quality control.** 106.91(a) *Nutrient testing to ensure that each batch of infant formula provides nutrients in accordance with Sec. 107.100.* Manufacturers shall test each batch as follows:	**Subpart C--Quality Control Procedures** **106.91 General quality control.** 106.91(a) *Nutrient testing to ensure that each batch of infant formula provides nutrients in accordance with Sec. 107.100.* Manufacturers or responsible parties shall test each batch as follows:

IFC Redlined Version

106.91(a) *Nutrient testing to ensure that each batch of infant formula provides nutrients in accordance with Sec. 107.100.* Manufacturers or responsible parties shall test each batch as follows:

IFC Comment

See the IFC General Comment regarding Definition of Manufacturer.

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FDA Proposed Regulation	IFC Suggested Language
106.91(a)(1) Each nutrient premix used in the manufacture of an infant formula shall be tested for each nutrient that the manufacturer is relying on the premix to provide to ensure that the premix is in compliance with the manufacturer's specifications;	Acceptable as proposed.
106.91(a)(2) During the manufacturing process, after the addition of the premix, or at the final-product-stage but before distribution, each batch of infant formula shall be tested for at least one indicator nutrient for each of the nutrient premixes used in the infant formula to confirm that the nutrients supplied by each of the premixes are present, in the proper concentration, in the batch of infant formula.	Acceptable as proposed.
106.91(a)(3) At the final-product-stage, before distribution of an infant formula, each batch shall be tested for vitamins A, C, E, and thiamin.	Acceptable as proposed.
106.91(a)(4) During the manufacturing process or at the final-product-stage, before distribution, each batch shall be tested for all nutrients required to be included in such formula under Sec. 107.100 of this chapter and for any nutrient added by the manufacturer for which testing is not conducted for compliance with paragraphs (a)(1) or (a)(3) of this section.	106.91(a)(4) During the manufacturing process or at the final-product-stage, before distribution, each batch shall be tested for each nutrient required to be included in such formula under 107.100 of this chapter if the presence of that nutrient in the batch has not been confirmed pursuant to testing conducted for compliance with paragraphs (a)(1), (a)(2) or (a)(3) of this section. Such testing shall be conducted using validated test methods.

IFC Redlined Version

106.91(a)(4) During the manufacturing process or at the final-product-stage, before distribution, each batch shall be tested for ~~all nutrients~~ each nutrient required to be included in such formula under 107.100 of this chapter ~~and for any nutrient added by the manufacturer for which testing is not~~ if the presence of that nutrient in the batch has not been confirmed pursuant to testing conducted for compliance with paragraphs (a)(1), (a)(2) or (a)(3) of this section. Such testing shall be conducted using validated test methods.

IFC Comment

The IFC suggests several changes to this required testing language. The Infant Formula Act is soundly based on the principle that infant formulas must be extensively tested to confirm that they contain nutrients in conformance with the nutrient table requirements. It would seem advisable, accordingly, to require the use of validated nutrient test methods to ensure the accuracy and precision of test results to determine compliance to the Act. While the Agency has included several proposals for validation of equipment, software and systems in proposed 106.35, most of which seem unnecessary to the IFC, the requirement for validated test methods is noticeably missing. To assure that the nutrient requirements of the Act are met with a high degree of confidence, the Agency should address methods validation in the final regulation.

The language suggested by the IFC above attempts to make clearer the testing

requirements for nutrients in premixes. The IFC interprets and agrees with FDA's intent to allow manufacturers or responsible parties to rely on testing pursuant to (a)(1) (as part of a premix), i.e., that finished product retesting for nutrients confirmed as part of (a)(1) premix testing is unnecessary pursuant to this section. Suggested addition of the phrase, "if the presence of that nutrient in the batch has not been confirmed pursuant to testing" above attempts to clarify that intent.

The IFC also believes that testing pursuant to (a)(2) should not be omitted from the list of prior testing recognized as sufficient to avoid finished product testing. The inclusion of (a)(2) is essential because (a)(1) alone would only confirm that a nutrient was present at the appropriate level in the premix, not that it was also present at the appropriate level in the formula itself.

Finally, the IFC sees no added benefit to the testing of nutrients not already listed in section 107.100, and has suggested its removal here, consistent with the charges already suggested for section 106.3(m) the definition of "nutrient."

Additionally, FDA's April announcement of the reopening of the comment period requested comments on the specific changes in current activities that would be required for companies to comply with proposal. All nutrients required to be included in infant formula under section 107.100 are currently being verified through testing. If FDA requires that all nutrients added by the manufacturer need to be tested, even where no quantity is declared on the label, this would add significant costs for additional laboratory facilities, tests and personnel to confirm their presence.

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FDA Proposed Regulation	IFC Suggested Language
106.91(b) *Stability testing.* Every 3 months, manufacturers shall collect representative samples from the final-product-stage of one batch of each physical form (powder, ready-to-feed, or concentrate) of each infant formula, at each manufacturing facility. The manufacturer shall test these samples for each nutrient required under Sec. 107.100 of this chapter and for any nutrient added by the manufacturer. The frequency of such testing shall be at the beginning, midpoint, and end of the shelf life of the infant formula and, depending on the nutrient and its stability within the matrix of the formulation, with additional frequency as is necessary to ensure that such formula complies with section 412 of the Federal Food, Drug, and Cosmetic Act (the act) throughout the shelf life of the infant formula; except that:	106.91(b) *Testing of finished product to confirm that the infant formula provides nutrients in accordance with Sec. 107.100.* Manufacturers or responsible parties shall test finished product as follows: 106.91(b)(1) *Periodic Analysis.* Every 3 months, manufacturers or responsible parties shall collect representative samples of infant formula of one batch of each physical form (powder, ready-to-feed, or concentrate) of each infant formula, at each manufacturing facility. The manufacturer shall test these samples for each nutrient required under Sec. 107.100 of this chapter that was not tested directly at the finished product stage pursuant to 106.91(a)(4). 106.91(b)(2) *Stability testing.* Using representative samples collected from finished product batches, the manufacturer shall conduct stability analysis for selected labile nutrients with sufficient frequency to substantiate the maintenance of nutrient content consistent with section 412 of the Federal Food, Drug, and Cosmetic Act (the act) throughout the shelf life of the infant formula.

IFC Redlined Version

106.91(b) ~~*Stability testing*~~ *Testing of finished product to confirm that the infant formula provides nutrients in accordance with Sec. 107.100.* Manufacturers or responsible parties shall test finished product as follows:

106.91(b)(1) *Periodic Analysis.* Every 3 months, manufacturers or responsible parties shall collect representative samples ~~from the final-product-stage~~ of infant formula of one batch of each physical form (powder, ready-to-feed, or concentrate) of each infant formula, at each manufacturing facility. The manufacturer shall test these samples for each nutrient required under Sec. 107.100 of this chapter ~~and for any nutrient added by the manufacturer. The frequency of such testing shall be at the beginning, midpoint, and end of~~ that was not tested directly at the finished product stage pursuant to 106.91(a)(4).

106.91(b)(2) *Stability testing.* Using representative samples collected from finished product batches, the manufacturer shall conduct stability analysis for selected labile nutrients ~~The frequency of such testing shall be at the beginning, midpoint, and end of~~ with sufficient frequency to substantiate the maintenance of nutrient content consistent ~~throughout the shelf life of the infant formula and, depending on the nutrient and its stability within the matrix of the formulation, with additional frequency as is necessary to ensure that such formula complies~~ with section 412 of the Federal Food, Drug, and Cosmetic Act (the act) throughout the shelf life of the infant formula.~~; except that:~~

IFC Comment

The current infant formula quality control regulations distinguish between testing

performed as a Periodic Analysis (106.30(b)(2)) and as a Stability Analysis (106.30(b)(3)). This distinction makes sense. These two testing regimens serve different purposes, and each has worked independently and effectively over the past decade to provide additional assurances that required nutrients are present within required ranges in infant formula.

Periodic analyses serve as a quarterly check that the controls used to assure the presence of all required nutrients within required ranges in the finished infant formula are appropriate. Stability analyses, on the other hand, serve as a check that labile nutrients (i.e., those that tend to degrade over time) present in infant formula at the finished product stage do not, over the shelf life of the formula, degrade below minimum levels. Infant formula manufacturers are required to test finished products for all nutrients initially and then evaluate for stability at the end of shelf life. In the new proposal, all nutrients would need to be tested at a minimum of the beginning, middle and end of shelf life to substantiate the nutrient content. This additional testing of all nutrients in addition to the added time point during the shelf life will require additional personnel, capital and yearly operating expenses without any real benefit.

FDA's proposal has two major problems, however: it combines the two types of testing inappropriately and the stability testing proposal requires an excessive number of infant formulas and nutrients to be routinely analyzed. The IFC feels that it is inappropriate and unwarranted to combine these two different types of testing. Although the results of testing generated pursuant to Periodic Analyses can also be used as the "beginning" results for Stability Analyses, that is the only logical overlap between the two. With regard to stability testing, because manufacturers typically produce more than one variation of a single infant formula product, as well as multiple presentation sizes, the samples required to be set aside for quarterly stability testing could run into the hundreds.

Because the IFC feels that combining the two types of testing introduces unwarranted and burdensome additional testing into each other, the IFC suggests separating proposed 106.91(b) into two subparagraphs: (b)(1) and (b)(2), Periodic Analyses and Stability Testing, respectively, and making the additional changes discussed below.

As separated, the requirement to conduct Periodic Analyses is straightforward. Quarterly, a manufacturer or responsible party must test a finished batch of each form of infant formula (in each facility) for all nutrients not analyzed directly in the immediate analysis of that batch. With respect to stability testing, the IFC submits that the current regulation requiring stability analyses, 106.30(b)(3), incorporates all the needed safeguards to assure that infant formula provides required nutrients within required ranges over the labeled shelf life of the infant formula. The IFC's proposed language simply incorporates the wording of current 106.30(b)(3) into the proposed testing regimen.

While the IFC believes that its suggested revisions to the proposal are justified, the discussion that follows addresses the shortcomings that it perceives exist in the stability testing contained in FDA's proposal. As proposed, stability testing would add significantly to the cost of infant formula by requiring that "all" nutrients be tested throughout shelf life, not just the ones that are subject to degradation or other change. Adding to the cost of infant formula by mandating manufacturers or responsible parties to test for nutrients a) that are known to be in the product (from results of the Periodic Analysis and other testing) and b) do not degrade, even under extreme conditions of storage, cannot be justified.

Attached are nutritional profiles of infant formula provided to FASEB. (Attachment O). They demonstrate the IFC's point that stability testing for nondegradable nutrients known to be present in the product at the start of stability testing will yield no new information and simply add cost to the product without adding value. These results, which were developed by the IFC in the context of FASEB's review of nutrient requirements for infant formula, show that certain nutrients are known not to degrade in infant formula.

The IFC acknowledges the concern expressed by the Agency in the preamble that "selected nutrients" may be chosen for analyses based on past experience, but that a new infant formula may change the assumptions. This concern is adequately addressed with the remaining requirement to test the initial batch of a new infant formula for all nutrients, and to test it annually thereafter up to the end of its shelf life. The IFC believes that this testing is appropriate for new infant formulas to guard against these unexpected changes in assumptions; however, it is not appropriately applied to infant formulas for which the manufacturer has experience.

See the IFC General Comment regarding Definition of Manufacturer for the justification for adding "or responsible parties" after "manufacturer" in appropriate places.

FDA Proposed Regulation	IFC Suggested Language
106.91(b)(1) If the infant formula is a new infant formula, manufacturers shall collect a representative sample from the final-product-stage of each physical form (powder, ready-to-feed, or concentrate) of the first batch of the new infant formula and test these samples according to the requirements of this section; and	106.91(b)(3) If the infant formula is a new infant formula, manufacturers or responsible parties shall collect a representative sample from the final-product-stage of each physical form (powder, ready-to-feed, or concentrate) of the first batch of the new infant formula and test these samples according to the requirements of this section; and

IFC Redlined Version

106.91(b)(~~1~~3) If the infant formula is a new infant formula, manufacturers or responsible parties shall collect a representative sample from the final-product-stage of each physical form (powder, ready-to-feed, or concentrate) of the first batch of the new infant formula and test these samples according to the requirements of this section; and

IFC Comment

See the IFC General Comment regarding Definition of Manufacturer.

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FDA Proposed Regulation	IFC Suggested Language
106.91(b)(2) If an infant formula has been changed in formulation or in processing in a way that does not make it a new infant formula but that may affect whether it is adulterated under section 412(a) of the act, the manufacturer shall collect a representative sample from the final-product-stage of each physical form (powder, ready-to-feed, or concentrate) of the first batch of the infant formula and shall test these samples according to the frequency required by this section for each nutrient that has been or may have been affected by the change.	106.91(b)(4) If an infant formula has been changed in formulation or in processing in a way that does not make it a new infant formula but that may affect whether it is adulterated under section 412(a) of the act, the manufacturer or responsible party shall collect a representative sample from the final-product-stage of each physical form (powder, ready-to-feed, or concentrate) of the first batch of the infant formula and shall test these samples for each nutrient that has been or may have been significantly and adversely affected by the change. The manufacturer or responsible party shall determine if stability testing should be conducted for such a change and the frequency of such testing, if deemed necessary.

IFC Redlined Version

106.91(b)(~~2~~4) If an infant formula has been changed in formulation or in processing in a way that does not make it a new infant formula but that may affect whether it is adulterated under section 412(a) of the act, the manufacturer or responsible party shall collect a representative sample from the final-product-stage of each physical form (powder, ready-to-feed, or concentrate) of the first batch of the infant formula and shall test these samples ~~according to the frequency required by this section~~ for each nutrient that has been or may have been significantly and adversely affected by the change. The manufacturer or responsible party shall determine if stability testing should be conducted for such a change and the frequency of such testing, if deemed necessary.

IFC Comment

See the IFC General Comment regarding Definition of Manufacturer.

As noted in the IFC's comment above, stability testing is not justified for several non-labile nutrients. For changes identified in this paragraph, which under proposed 106.140 may have no expected impact on nutrients at all, it should be left to the manufacturer to determine whether stability testing is justified and, if so, its frequency. Thus, even if a change possibly could affect the level of a mineral, it is sufficient to test for it and confirm its presence at required levels in the finished product; continuing to confirm its known presence throughout shelf life is not necessary, since minerals do not degrade.

Infant formula manufacturers currently evaluate all changes to formulation or processing of an infant formula. In that assessment they determine if the change will affect the nutrient content of the formulation and if so, notify the FDA. In the preamble of the proposed GMP's, FDA has provided examples of changes they would consider notifiable changes and requiring testing at the required intervals. If the manufacturer is now required to complete nutrient testing on additional changes as described in the preamble, additional personnel will be needed to complete this testing. As stated previously, stability testing is not justified for several non-labile nutrients. For changes identified in this paragraph, which under proposed 106.140 may have no expected impact on nutrients at all, it should be left to the manufacturer to determine whether stability testing is justified and, if so, its frequency.

FDA Proposed Regulation	IFC Suggested Language
106.91(c) Quality control records. Manufacturers shall make and retain quality control records in accordance with Sec. 106.100(e)(5)(i) and (f)(7).	Acceptable as proposed.
106.92 Audits of quality control procedures. A manufacturer of an infant formula, or an agent of such a manufacturer, shall conduct regularly scheduled audits to determine whether the manufacturer has complied with the quality control procedures that are necessary to ensure that an infant formula provides nutrients in accordance with section 412(b) and (i) of the Federal Food, Drug, and Cosmetic Act and is manufactured in a manner designed to prevent adulteration of the infant formula under section 412(a)(1) and (a)(3) of the Federal Food, Drug, and Cosmetic Act. These audits shall be performed by an individual who, as a result of education, training, and experience, is knowledgeable in all aspects of infant formula production and of the agency's regulations concerning quality control procedures but who has no direct responsibility for the matters being audited.	**106.92 Audits of quality control procedures.** A manufacturer, or an agent thereof, shall conduct regularly scheduled audits, according to its established practice, to determine whether the manufacturer has complied with the quality control procedures that are necessary to ensure that an infant formula provides nutrients in accordance with section 412(b) and (i) of the Federal Food, Drug, and Cosmetic Act and is manufactured in a manner designed to prevent adulteration of the infant formula under section 412(a)(1) and (a)(3) of the Federal Food, Drug, and Cosmetic Act. These audits shall be performed by an individual who, as a result of education, training, and experience, is knowledgeable of infant formula production and of the agency's regulations concerning quality control procedures but who has no direct responsibility for the matters being audited.

IFC Redlined Version

106.92 Audits of quality control procedures.

A manufacturer ~~of an infant formula~~, or an agent ~~of such a manufacturer~~ thereof, shall conduct regularly scheduled audits, according to its established practice, to determine whether the manufacturer has complied with the quality control procedures that are necessary to ensure that an infant formula provides nutrients in accordance with section 412(b) and (i) of the Federal Food, Drug, and Cosmetic Act and is manufactured in a manner designed to prevent adulteration of the infant formula under section 412(a)(1) and (a)(3) of the Federal Food, Drug, and Cosmetic Act. These audits shall be performed by an individual who, as a result of education, training, and experience, is knowledgeable ~~in all aspects~~ of infant formula production and of the agency's regulations concerning quality control procedures but who has no direct responsibility for the matters being audited.

IFC Comments

FDA's April announcement of the reopening of the comment period requested comments on the specific changes in current activities that would be required for companies to comply with proposal. The auditor is expected to possess a general knowledge of the aspects of infant formula production, however they need not have knowledge to the depth and extent that the use of the word "all" in the proposal may imply. Such knowledge would entail years of cross training and constant retraining. Auditors are currently knowledgeable on a wide scope of infant formula production aspects, including raw materials, blending/mixing, processing, standardization, filling, sterilization/drying, packing, warehousing, shipping, maintenance, cleaning, lab testing, documentation control, batch

record review/release, training, etc., as well as how to conduct routine audits. We note that the proposed regulation acknowledges that past experience in infant formula production may be relevant, even though the auditor may have no current responsibility for the activities being audited.

Because this proposed requirement is very similar to 106.90, please refer to the IFC's comment to that proposed section. The IFC requests that the same changes as recommended in 106.90 be incorporated in this section. In addition, we have suggested language clarifying that it is the manufacturer's responsibility to determine what will constitute "regularly scheduled audits" and to establish SOPs for that purpose to which it will adhere.

FDA Proposed Regulation	IFC Suggested Language
Subpart D--Conduct of Audits. **106.94 Audit plans and procedures.** 106.94(a) Manufacturers shall develop and follow a written audit plan that is available at the manufacturing facility for FDA inspection.	**Subpart D--Conduct of Audits.** **106.94 Audit plans and procedures.** Acceptable as proposed.
106.94(b) The audit plan shall include audit procedures that set out the methods the manufacturer uses to determine whether the facility is operating in accordance with current good manufacturing practice, with the quality control procedures that are necessary to assure that an infant formula provides nutrients in accordance with section 412(b) and (i) of the Federal Food, Drug, and Cosmetic Act, and in a manner designed to prevent adulteration of the infant formula.	106.94(b) The audit plan shall include audit procedures that set out the methods the manufacturer or responsible party uses to determine whether the facility is operating in accordance with current good manufacturing practice, with the quality control procedures that are necessary to assure that an infant formula provides nutrients in accordance with section 412(b) and (i) of the Federal Food, Drug, and Cosmetic Act, and in a manner designed to prevent adulteration of the infant formula.

IFC Redlined Version

106.94(b) The audit plan shall include audit procedures that set out the methods the manufacturer or responsible party uses to determine whether the facility is operating in accordance with current good manufacturing practice, with the quality control procedures that are necessary to assure that an infant formula provides nutrients in accordance with section 412(b) and (i) of the Federal Food, Drug, and Cosmetic Act, and in a manner designed to prevent adulteration of the infant formula.

IFC Comment

See the IFC General Comment regarding Definition of Manufacturer.

FDA Proposed Regulation	IFC Suggested Language
106.94(c) The audit procedures shall include, but not be limited to:	Acceptable as proposed.
106.94(c)(1) An evaluation of the production and in-process control system established under Sec. 106.6(b) by:	Acceptable as proposed.
106.94(c)(1)(i) Observing the production of infant formula and comparing the observed process to the written production and in-process control plan required under Sec. 106.6(b);	106.94(c)(1)(i) Observing the critical manufacturing steps of infant formula and comparing the observed process to the written production and in-process control plan required under Sec. 106.6(b);

IFC Redlined Version

106.94(c)(1)(i) Observing the ~~production~~ critical manufacturing steps of infant formula and comparing the observed process to the written production and in-process control plan required under Sec. 106.6(b);

IFC Comment

This proposal requires the audit to include the observation of infant formula production and comparing it to the written control plan. This could be interpreted as requiring observation of every single manufacturing operation, from ingredient receipt, through manufacturing, holding and distribution. Such detail during an audit would make the auditing process an extremely tedious and unwieldy endeavor, and would result in overly prolonged audits. Auditing may take weeks to accomplish at this detail. It is also unnecessary, because such comparisons can be made from less intrusive and resource intensive reviews, such as spot-checking some operations, while reviewing others based on production records, interviews, etc.

FDA's April announcement of the reopening of the comment period requested comments on the specific changes in current activities that would be required for companies to comply with proposal. This change would require additional trained personnel to complete this type of audit, and it would interfere unnecessarily with the focus on high quality production.

FDA Proposed Regulation	IFC Suggested Language
106.94(c)(1)(ii) Reviewing records of the monitoring of points, steps, or stages where control is deemed necessary to prevent adulteration; and	106.94(c)(1)(ii) Reviewing records of representative batches, over multiple days of production, of the monitoring of points, steps, or stages where control is critical to prevent adulteration; and

IFC Redlined Version

106.94(c)(1)(ii) Reviewing records of representative batches, over multiple days of production, of the monitoring of points, steps, or stages where control is ~~deemed necessary~~ critical to prevent adulteration; and

IFC Comment

The preamble to this proposed section states that the review of "production and in-process control records" contemplated by this section must involve "all batches produced in a given period of time." Such a requirement could be overwhelming unless it involved a very short time span. The IFC feels that audits would be more thorough and beneficial if the record review covered a wider span of time (i.e., months), but included "representative" batches, as opposed to "all" batches, and "representative" records of the most important control points, i.e., critical points.

FDA Proposed Regulation	IFC Suggested Language
106.94(c)(1)(iii) Reviewing records of how deviations from any standard or specification at points, steps, or stages where control is deemed necessary to prevent adulteration were handled; and	106.94(c)(1)(iii) Reviewing records of how deviations from any specification at points, steps, or stages where control is deemed necessary to prevent adulteration were handled to assure that the review was complete; and

IFC Redlined Version

106.94(c)(1)(iii) Reviewing records of how deviations from any ~~standard or~~ specification at points, steps, or stages where control is deemed necessary to prevent adulteration were handled ~~to assure that the review was complete~~; and

IFC Comment

See the IFC General Comment regarding Specifications.

The preamble to this proposal states that the auditor must review the responses to the deviations to determine "... whether the conclusions and follow-up of these investigations are appropriate for each failure to meet the specification or standard." This is a significantly different responsibility than that suggested by the proposed language of the regulation. Although the IFC believes that an auditor must be well schooled in product quality, it is unrealistic to expect that an auditor will have the breadth of technical knowledge and background to assess whether the dispositions, which may involve multiple disciplines in a company, are "appropriate." A more reasonable expectation is that the auditor's review confirms the completeness and sufficiency of review of the deviations, rather than trying to determine if the conclusions and follow-up were appropriate. The language suggested by the IFC aims at this distinction, and the preamble to the final regulation should also reflect this point to remove any misimpressions that the proposal's preamble language may have created.

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FDA Proposed Regulation	IFC Suggested Language
106.94(c)(2) A review of a representative sample of all records maintained in accordance with Sec. 106.100(e) and (f).	Acceptable as proposed.
Subpart E--Quality Factors for Infant Formulas **106.96 Quality factors in infant formulas.** 106.96(a) All infant formulas shall, when fed to infants as a sole source of nutrition, be of sufficient quality to meet the nutritional requirements for healthy growth. The regulations set forth in this subpart define the minimum quality factors for infant formulas.	**Subpart E--Quality Factors for Infant Formulas** **106.96 Quality factors in infant formulas.** 106.96(a) All infant formulas shall meet established quality factors.

IFC Redlined Version

106.96(a) All infant formulas shall meet established quality factors~~, when fed to infants as a sole source of nutrition, be of sufficient quality to meet the nutritional requirements for healthy growth. The regulations set forth in this subpart define the minimum quality factors for infant formulas~~.

IFC Comment

For the reasons discussed in detail previously, there are legal, scientific and policy issues supporting the IFC position that it is inappropriate to establish "healthy growth" or "normal growth" as a quality factor. The proposal would have required clinical studies to demonstrate the quality factor of "healthy growth." Although we believe that it is inappropriate to set a quality factor for "healthy growth," we do recognize that there are some instances when a clinical study is needed. Importantly, the 1986 Guidelines recognize that the manufacturer is in the best position to assess when a clinical study is needed. IFC supports the principles in the 1986 Guidelines, which address clinical studies in the premarket notification section. Thus, IFC believes that clinical studies should be addressed in section 106.120, which sets forth the data and information that must be submitted in a premarket notification. There are almost two decades of industry experience of submitting clinical studies, not for purposes of supporting a quality factor for "growth," but when necessary for providing the Agency with the assurance of nutritional adequacy of the new infant formula.

IFC reiterates its position with regard to the impropriety of establishing "healthy" or "normal growth" as a quality factor. The following comments on the proposed rule are offered, nevertheless, to inform any incorporation of the proposed language into an agency Guidance document for those situations in which it is determined that a clinical demonstration of growth is the most appropriate way to demonstrate bioavailability. IFC suggests adding the phrase "in the infant population for which they are intended" to accommodate special infant formulas. The IFC also recommends that the phrase "when fed to infants as a sole source of nutrition" be moved to consideration for inclusion in the Guidance.

The IFC also submits that the term "healthy growth" should be changed to "expected physical growth" throughout the current proposal when translated into a Guidance.

"Expected" is the more meaningful term, and the only practical way of assessing growth is by physical measurement. It should also be noted here that attempts have been made in the past to define, even more specifically and quantitatively, what constitutes normal physical growth -- e.g., the AAP consultation's discussion of an acceptable divergence of the mean growth velocity of the experimental group from that of the control group. Further, the IFC agrees with FDA's apparent conclusion that it would be unwise to establish quantitative standards at this time, given the evolving scientific understanding of what is "expected," "normal" or even "optimal" in this area.

As explained in the General Comments, the Infant Formula Act does not actually mention "healthy growth" -- or even "normal growth," used elsewhere in the proposed regulations. Moreover, the Infant Formula Act does not define "quality factors" except to say "Quality factors pertain to the bioavailability of a nutrient and the maintenance of level or potency of nutrients through an expected shelf life of the product."[5] Although, as responsible manufacturers, the industry accepts the responsibility of producing formulas that provide sufficient and bioavailable nutrition, industry strongly objects to establishing "growth," per se, as a quality factor and to the indiscriminate application of any such requirement. IFC is also concerned about the Agency's tentative conclusion in the preamble that "on a case-by-case basis additional quality factors may be needed for a specific formula product." Any such effort to accomplish case-by-case quality factors would be flawed, because such factors can only be established by notice and comment rulemaking. Furthermore, regulatorily imposed quality factors extending beyond bioavailability and sufficiency throughout shelf life were clearly not intended by Congress.

The IFC supports the Agency's offer to provide clinical guidance. Our key point, however, is that clinical studies are not the only way to demonstrate bioavailability, and that other evidence may often be equally convincing and more appropriate.

FDA Proposed Regulation	IFC Suggested Language
106.96(b) All infant formulas shall be capable of supporting normal physical growth of infants.	Delete.

IFC Redlined Version

~~106.96(b) All infant formulas shall be capable of supporting normal physical growth of infants.~~

IFC Comment

Again, IFC objects to this requirement for the reasons already stated. IFC offers the following comments on the language as proposed, however, in case similar concepts are incorporated into agency Guidance.

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[5] *See* House Committee on Interstate and Foreign Commerce Report: The Infant Formula Act, p. 6.

FDA Proposed Regulation	IFC Suggested Language
106.96(c) All infant formulas shall be formulated and manufactured such that the protein is of sufficient biological quality to meet the protein requirements of infants.	Acceptable; Renumbered to 106.96(b).
106.97 Assurances for quality factors. 106.97(a) General quality factor of normal physical growth.	**106.97 Assurances for quality factors.** Delete.

IFC Redlined Version

106.96(cb) All infant formulas shall be formulated and manufactured such that the protein is of sufficient biological quality to meet the protein requirements of infants.

~~106.97(a) General quality factor of normal physical growth.~~

IFC Comment

See General Comments on Assessment of Normal Growth.

FDA Proposed Regulation	IFC Suggested Language
106.97(a)(1) The manufacturer shall conduct an adequate and well-controlled clinical study, in accordance with good clinical practice, to determine whether an infant formula supports normal physical growth in infants when the formula is fed as the sole source of nutrition.	Delete.

IFC Redlined Version

~~106.97(a)(1) The manufacturer shall conduct an adequate and well-controlled clinical study, in accordance with good clinical practice, to determine whether an infant formula supports normal physical growth in infants when the formula is fed as the sole source of nutrition.~~

IFC Comment

See General Comments on Assessment of Normal Growth. IFC offers the following comments with the caveat that clinical growth studies should be conducted for the purpose of demonstrating bioavailability only when they are the most appropriate such demonstration, and that any specifics as to the nature and scope of such a study should be incorporated into agency Guidance rather than a regulation.

See the IFC General Comment regarding Definition of Manufacturer. As explained in our comments to sections 106.3(j) and 106.3(s), primary infant formula manufacturers sometimes rely on other manufacturers to handle specific phases of the manufacture of a given formula. In such a situation, only the primary manufacturer would be expected to conduct a clinical study or other assurances of quality factors. We have suggested, in our